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Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults (Review)

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[Intervention Review]

Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder characterised by inattention, hyperactivity, and impulsivity. ADHD can persist into adulthood and can affects individuals' social and occupational functioning, as well as their quality of life and health. ADHD is frequently associated with other mental disorders such as substance use disorders and anxiety and affective disorders. Amphetamines are used to treat adults with ADHD, but uncertainties about their efficacy and safety remain.

Objectives

To examine the efficacy and safety of amphetamines for adults with ADHD.

Search methods

In August 2017, we searched CENTRAL, MEDLINE, Embase, PsycINFO, 10 other databases, and two trials registers, and we ran citation searches for included studies. We also contacted the corresponding authors of all included studies, other experts in the field, and the pharmaceutical company, Shire, and we searched the reference lists of retrieved studies and reviews for other published, unpublished, or ongoing studies. For each included study, we performed a citation search in Web of Science to identify any later studies that may have cited it.

Selection criteria

We searched for randomised controlled trials comparing the efficacy of amphetamines (at any dose) for ADHD in adults aged 18 years and over against placebo or an active intervention.

Data collection and analysis

Two review authors extracted data from each included study. We used the standardised mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias. We rated the quality of the evidence using the GRADE approach, which yielded high, moderate, low, or very low quality ratings based on evaluation of within-trial risk of bias, directness of evidence, heterogeneity of data; precision of effect estimates, and risk of publication bias.

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Main results

We included 19 studies that investigated three types of amphetamines: dexamphetamine (10.2 mg/d to 21.8 mg/d), lisdexamfetamine (30 mg/d to 70 mg/d), and mixed amphetamine salts (MAS; 12.5 mg/d to 80 mg/d). These studies enrolled 2521 participants; most were middle-aged (35.3 years), Caucasian males (57.2%), with a combined type of ADHD (78.8%). Eighteen studies were conducted in the USA, and one study was conducted in both Canada and the USA. Ten were multi-site studies. All studies were placebo-controlled, and three also included an active comparator: guanfacine, modafinil, or paroxetine. Most studies had short-term follow-up and a mean study length of 5.3 weeks.

We found no studies that had low risk of bias in all domains of the Cochrane 'Risk of bias' tool, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment, but also because we noted attrition bias, and because we could not rule out the possibility of a carry-over effect in studies that used a cross-over design.

Sixteen studies were funded by the pharmaceutical industry, one study was publicly funded, and two studies did not report their funding sources.

Amphetamines versus placebo

Severity of ADHD symptoms: we found low- to very low-quality evidence suggesting that amphetamines reduced the severity of ADHD symptoms as rated by clinicians (SMD −0.90, 95% confidence interval (CI) −1.04 to −0.75; 13 studies, 2028 participants) and patients (SMD −0.51, 95% CI −0.75 to −0.28; six studies, 120 participants).

Retention: overall, we found low-quality evidence suggesting that amphetamines did not improve retention in treatment (risk ratio (RR) 1.06, 95% CI 0.99 to 1.13; 17 studies, 2323 participants).

Adverse events: we found that amphetamines were associated with an increased proportion of patients who withdrew because of adverse events (RR 2.69, 95% CI 1.63 to 4.45; 17 studies, 2409 participants).

Type of amphetamine: we found differences between amphetamines for the severity of ADHD symptoms as rated by clinicians. Both lisdexamfetamine (SMD −1.06, 95% CI −1.26 to −0.85; seven studies, 896 participants; low-quality evidence) and MAS (SMD −0.80, 95% CI −0.93 to −0.66; five studies, 1083 participants; low-quality evidence) reduced the severity of ADHD symptoms. In contrast, we found no evidence to suggest that dexamphetamine reduced the severity of ADHD symptoms (SMD −0.24, 95% CI −0.80 to 0.32; one study, 49 participants; very low-quality evidence). In addition, all amphetamines were efficacious in reducing the severity of ADHD symptoms as rated by patients (dexamphetamine: SMD −0.77, 95% CI −1.14 to −0.40; two studies, 35 participants; low-quality evidence; lisdexamfetamine: SMD −0.33, 95% CI −0.65 to −0.01; three studies, 67 participants; low-quality evidence; MAS: SMD −0.45, 95% CI −1.02 to 0.12; one study, 18 participants; very low-quality evidence).

Dose at study completion: different doses of amphetamines did not appear to be associated with differences in efficacy.

Type of drug-release formulation: we investigated immediate- and sustained-release formulations but found no differences between them for any outcome.

Amphetamines versus other drugs

We found no evidence that amphetamines improved ADHD symptom severity compared to other drug interventions.

Authors' conclusions

Amphetamines improved the severity of ADHD symptoms, as assessed by clinicians or patients, in the short term but did not improve retention to treatment. Amphetamines were associated with higher attrition due to adverse events. The short duration of studies coupled with their restrictive inclusion criteria limits the external validity of these findings. Furthermore, none of the included studies had an overall low risk of bias. Overall, the evidence generated by this review is of low or very low quality.

PLAIN LANGUAGE SUMMARY

Amphetamines for attention deficit hyperactivity disorder in adults

Background

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Attention deficit hyperactivity disorder (ADHD) is a childhood-onset psychiatric disorder that can persist into adulthood in up to 50% of patients. From a clinical point of view, ADHD is characterised by hyperactivity, mood instability, irritability, difficulties in maintaining attention, lack of organisation, and impulsive behaviours. Occurrence of other disorders at the the same time is common, especially mood disorders and substance abuse. Amphetamines (a type of stimulant) are thought to improve ADHD symptoms, but there are concerns about how safe they are for regular use by patients with ADHD.

Review question

We examined whether treatment with amphetamines improves the symptoms of ADHD in adults.

Study characteristics

Reviewers found 19 studies, which enrolled 2521 patients. Most patients were male (57.2%), middle-aged (mean age 35.3 years) Caucasians (84.5%). These studies compared amphetamines to placebo (something that looks like an amphetamine but with no active ingredient), and three studies also compared amphetamines with other drugs such as guanfacine, modafinil, and paroxetine. In this review, we assessed the effects of three different kinds of amphetamines: dexamphetamine (from 10.2 to 21.8 mg/d), lisdexamfetamine (from 30 to 70 mg/d), and mixed amphetamine salts (MAS) (from 12.5 to 80 mg/d). Treatment length ranged from one to 20 weeks. Eighteen studies were conducted in the USA and one study in Canada and the USA. Ten studies were conducted at multiple sites. Study funding was reported in all but two studies. Sixteen studies were funded by the manufacturer, and one was funded by government agencies.

All amphetamines reduced the severity of ADHD symptoms as rated by patients. Lisdexamfetamine and MAS also reduced the severity of ADHD symptoms as rated by clinicians, but dexamphetamine did not. Overall, amphetamines did not make people more likely to stay in treatment and were associated with higher risk of treatment ending early as the result of adverse events. We found no evidence suggesting that higher doses worked better than lower ones. We did not find any difference in effectiveness between amphetamines that act for longer periods of time versus those that act for shorter periods of time. Therefore, it appears that short-term treatment with amphetamines reduces the severity of ADHD symptoms, but studies assessing the effects of amphetamines for longer periods of time are needed. We found no differences in effectiveness between amphetamines and guanfacine, modafinil, or paroxetine.

Quality of the evidence

The quality of the evidence was low to very low for all outcomes for several reasons, namely, it was possible for patients to know the treatment they were taking; the number of studies and included patients was low, leading to imprecise results for many outcomes; the studies had problems in their design; and, for some outcomes, results varied across trials.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Amphetamines versus placebo for attention deficit hyperactivity disorder (ADHD) in adults

Patient or population: adult patients with attention deficit hyperactivity disorder (ADHD)
Settings: outpatients
Intervention: amphetamines
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Amphetamines				
Dexamphetamine						
ADHD symptom severity: clinician rated Assessed with ADHD-RS-IV Follow-up: post intervention (mean 20 weeks)	-	Mean clinician-rated ADHD symptom severity score in the intervention groups was **0.24 standard deviations lower** (0.80 lower to 0.32 higher)	-	49 (1 study)	⊕◯◯◯ **Very low**[a,b,c]	An SMD of 0.24 can be considered a small effect size.
ADHD symptom severity: patient rated Assessed with DSM-IV ADHD Behavior Checklist for Adults Follow-up: post intervention (mean 2 weeks)	-	Mean patient-rated ADHD symptom severity score in the intervention groups was **0.77 standard deviations lower** (1.14 lower to 0.4 lower)	-	35 (2 studies)	⊕⊕◯◯ **Low**[a,c,d]	An SMD of 0.77 can be considered a medium effect size.
Lisdexamfetamine						

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ADHD symptom severity: clinician rated Assessed with ADHD-RS-IV and CAARS Follow-up: post intervention (1-10 weeks)	-	Mean clinician-rated ADHD symptom severity score in the intervention groups was **1.06 standard deviations lower** (1.26 lower to 0.85 lower)	-	896 (7 studies)	⊕⊕◯◯ **Low**[c,e,f,g]	An SMD of 1.06 can be considered a large effect size.
ADHD symptom severity: patient rated Assessed with CAARS Follow-up: post intervention (1-4 weeks)	-	Mean patient-rated ADHD symptom severity score in the intervention groups was **0.33 standard deviations lower** (0.65 lower to 0.01 lower)	-	67 (3 studies)	⊕⊕◯◯ **Low**[c,d,h]	An SMD of 0.33 can be considered a medium effect size.
Mixed amphetamine salts						
ADHD symptom severity: clinician rated Assessed with ADHD-RS-IV and AISRS Follow-up: post intervention (3-13 weeks)	-	Mean clinician-rated ADHD symptom severity score in the intervention groups was **0.80 standard deviations lower** (0.93 lower to 0.66 lower)	-	1083 (5 studies)	⊕⊕◯◯ **Low**[c,e]	An SMD of 0.8 can be considered a small effect size.
ADHD symptom severity: patient rated Assessed with CAARS Follow-up: post intervention (mean 1 week)	-	Mean patient-rated ADHD symptom severity score in the intervention groups was **0.45 standard deviations lower** (1.02 lower to 0.12 higher)	-	18 (1 study)	⊕◯◯◯ **Very low**[b,c,h]	An SMD of 0.45 can be considered a medium effect size.
All amphetamines						

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Retention in treatment Assessed with the proportion of randomised participants that completed the study Follow-up: post intervention (1-20 weeks)	**Study population**		**RR 1.06** (0.99 to 1.13)	2323 (17 studies)	⊕⊕◯◯ **Low**[a,i]	-
	708 per 1000	**750 per 1000** (701 to 800)				
	Moderate					
	800 per 1000	**848 per 1000** (792 to 904)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADHD: attention deficit hyperactivity disorder; **ADHD-RS-IV:** Attention Deficit Hyperactivity Disorder Rating Scale, Fourth Version; **AISRS:** Adult Attention Deficity Hyperactivity Disorder Investigator Rating Scale; **CAARS:** Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scales;**CI:** confidence interval; **DSM-IV:** *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* **SMD:** standardised mean difference.

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]The certainty of the evidence was downgraded by one level owing to unclear risk of detection and performance bias because it is unclear whether blinding can be achieved in placebo-controlled studies given the powerful behavioural effects of amphetamines.
[b]The certainty of the evidence was downgraded by two levels owing to imprecision because the 95% CI is wide, indicating that the intervention effect for this outcome can range from a small, worsening effect to a large benefit.
[c]The statistical power to detect publication bias for this comparison in this review is low.
[d]The certainty of the evidence was downgraded by one level owing to imprecision because the 95% CI is rather wide, indicating that the intervention effect for this outcome can range from a moderate to a large benefit.
[e]The certainty of the evidence was downgraded by two levels owing to unclear risk of detection and performance bias (it is unclear whether blinding can be achieved in placebo-controlled studies given the powerful behavioural effects of amphetamines), high risk of attrition bias (large proportion of participants discontinued treatment or differences between study groups in discontinuation rates), and high risk of other bias (such as the possibility of carry-over effect in cross-over studies without a washout phase).
[f]The certainty of the evidence was downgraded by one level owing to moderate statistical heterogeneity.

[g]The certainty of the evidence was upgraded by one level because a large and precise effect size was observed.

[h]The certainty of the evidence was downgraded by one level owing to unclear risk of detection and performance bias (it is unclear whether blinding can be achieved in placebo-controlled studies given the powerful behavioural effects of amphetamines) and high risk of other bias (such as the possibility of carry-over effect in cross-over studies without a washout phase).

[i]The certainty of the evidence was downgraded by one level owing to inconsistency (this comparison includes three different types of amphetamines at a wide range of doses, and the analysis showed moderate heterogeneity).

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BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 7% of children and adolescents worldwide (Thomas 2015). ADHD is reported to continue into adulthood in 15% to 50% of children given this diagnosis (Faraone 2006; Lara 2009). Factors associated with persistence of the disorder into adulthood are the presence of comorbidity, ADHD severity, and ADHD treatment (Caye 2016). The prevalence of ADHD in adults has been estimated at 2.5% to 5% (Simon 2009; Willcutt 2012).

Childhood ADHD is characterised by inattention, hyperactivity, and impulsivity. Inattention is often presented as distractibility, difficulty in sustaining attention on tasks or activities, trouble in organising tasks or activities, and forgetfulness. Hyperactivity and impulsivity are usually manifested as an inability to be still or to undertake quiet activities, being fidgety, talking excessively, or having trouble awaiting turns (Thapar 2016). The clinical characteristics of ADHD in adults are more subtle than in children, with hyperactivity and impulsivity often manifesting as restlessness and talkativeness (Kessler 2010; Kooij 2009). In addition, symptoms of emotional dysregulation, such as irritability, emotional lability, and emotional reactivity, are usually described in adults with ADHD (Corbisiero 2013; Retz 2012). Symptoms of ADHD thus vary across the lifespan, with improvements in hyperactivity and impulsivity usually observed (Kessler 2010). However, inattention is thought to remain unchanged, and executive functions are significantly altered (Riccio 2005). This leads to an inability to perform complex activities as a consequence of lack of activity planning, inadequate time management, high distractibility, and lack of attention (Riccio 2005). The cluster of ADHD symptoms includes the clinical expression of neuropsychological dysfunction in several executive functions, such as working memory and impulse inhibition (Schoechlin 2005), and in reward and motivation (Castellanos 2006; Sonuga-Barke 2008).

Adults with ADHD are at higher risk of developing comorbid psychiatric disorders such as anxiety and mood and substance use disorders (Kessler 2006). In addition, a high prevalence of antisocial personality disorder has been observed in this population (Biederman 2006; Young 2005). Particularly worrying is the prevalence of substance misuse amongst adults with ADHD, which has been reported to be twice as high as that of the general population (Biederman 2006; Levin 1998). Similarly, an inverse association has been found in patients with substance use disorders, in whom the estimated prevalence of ADHD is 23% (Van Emmerik-van Oortmerssen 2012). Adults with ADHD tend to have more social problems that affect their work and family life (Biederman 1993). Furthermore, they have poorer driving performance and are more frequently involved in car accidents (Barkley 2002). Recently, ADHD has been associated with increased mortality (Dalsgaard 2015).

ADHD is usually diagnosed using the criteria of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM) or the*International Classification of Diseases* (ICD). Diagnostic criteria differ between the DSM and the ICD, and these criteria have varied across different versions of the DSM. For example, to qualify for ADHD, both DSM-IV and DSM-IV-TR require that patients have six out of nine symptoms of inattention or hyperactivity/impulsivity, that these symptoms have begun before the age of seven years, and that they clearly impair social, academic, or occupational function in two or more settings. In contrast, the latest version of the DSM - DSM-5 - requires only five out of nine symptoms of inattention or hyperactivity/impulsivity that have begun before the age of 12 years and that interfere with social, academic, or occupational functioning in two or more settings, for adults to qualify for ADHD. In addition, and for the first time, DSM-5 allows a diagnosis of ADHD to be made in patients with autism spectrum disorder (ASD). For a diagnosis of ADHD based on ICD-10 criteria, six symptoms of inattention, three symptoms of hyperactivity, and one symptom of impulsivity that are present before the age of six years, and that impair social, academic, or occupational function in two or more settings, are needed. The presence of a comorbid ASD is incompatible with a diagnosis of ADHD according to ICD-10 diagnostic criteria.

Description of the intervention

Amphetamines are drugs, structurally related to catecholamines, that increase dopamine (DA) and norepinephrine (NE) concentrations at the synapse. In healthy individuals, these catecholaminergic actions result in psychostimulant effects (Hardman 2001). Because of their stimulant activity within the central nervous system, amphetamines have been studied for the treatment of several disorders, including narcolepsy (Nishino 2007), obesity (Ioannides-Demos 2005), amphetamine dependence (Shearer 2002), cocaine dependence (Castells 2016), and ADHD (Wilens 2003).

Use of amphetamines for the treatment of adults with ADHD has been increasing during the past decade and recently surpassed use of methylphenidate in the USA (Safer 2016). Different types of amphetamines are available for the treatment of ADHD, such as lisdexamfetamine, dexamphetamine (or dextroamphetamine), and mixed amphetamine salts (MAS), which contain d-amphetamine and l-amphetamine at a ratio of 3:1. Amphetamines are metabolised in the liver, and their half-lives are 10 to 15 hours for MAS (10 to 12 hours for d-amphetamine and 12 to 15 hours for l-amphetamine) and around 12 hours for dexamphetamine (Markowitz 2017). Lisdexamfetamine is a prodrug with a half-life of around 0.6 hours that is metabolised to dexamphetamine (Markowitz 2017). All amphetamine derivatives are administered orally. Lisdexamfetamine is administered once a day,

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and MAS and dextroamphetamine may be administered once or twice a day depending on the formulation (immediate-release versus extended-release) (Markowitz 2017). Recommended dosages range from 5 mg/d to 40 mg/d for MAS (FDA 2015a), from 30 mg/d to 70 mg/d for lisdexamfetamine (FDA 2015b), and from 5 mg/d to 40 mg/d for dexamphetamine (FDA 2007).

How the intervention might work

From a neurobiological perspective, ADHD is characterised by a hypofunction in frontal-striatal, cerebellar circuits that results in executive function impairment, including decreased attention and reduced ability to plan activities and inhibit inappropriate actions. A dysfunction in dopaminergic neurotransmission has been observed in these circuits. Amphetamines increase dopamine (DA) and norepinephrine (NE) concentrations at the synapse. Although the precise mechanism of action is not well understood, it seems that these drugs act on the dopamine transporter (DAT) and presumably cause inversion of the transport direction of DAT, resulting in an efflux of dopamine from the presynaptic neuron towards the synapse. Some have proposed that amphetamines get into the presynaptic neuron through the DAT and cause exocytosis of vesicles containing DA. In addition to increased DA release, amphetamines inhibit catecholamine metabolism through catechol-O-methyltransferasse (COMT) (for a review of the mechanism of action of amphetamines, see Carboni 2004; Fleckenstein 2007; Heal 2013; and Sulzer 2005). Thus, by promoting DA release from the presynaptic neuron and inhibiting COMT, amphetamines increase dopamine at the synapse, which yields improvement in executive function and ADHD symptoms (for a review of the neurobiological basis of ADHD and the mechanism of action of psychostimulants, see Arnsten 2006; Grace 2002; Heal 2013; and Swanson 2007).

Why it is important to do this review

The number of medicines containing amphetamines and the number of clinical trials assessing the efficacy of these medicines for adults with ADHD have been increasing over past decades (Cunill 2016; Heal 2013). Furthermore, prescription of amphetamines for adults with ADHD has also increased (Safer 2016). In addition, after publication of the first version of this review in 2011 (Castells 2011a), lisdexamfetamine was approved for the treatment of adults with ADHD in several European countries (Ermer 2016; MHRA 2015). Despite this increase in the number of clinical trials and prescriptions of amphetamines, no new systematic review has focused on the efficacy of amphetamines in adults.

A number of factors appear to modify the efficacy of drugs used to treat ADHD. For instance, the efficacy of other stimulants seems to be lower in patients with ADHD and comorbid substance use disorders (Cunill 2015; Koesters 2008), implying that stimulants may be less useful in these patients and thus stressing the importance of adapting ADHD treatment to patient characteristics. Furthermore, the efficacy of methylphenidate is lower with lower doses (Castells 2011b; Faraone 2004), as well as with long-acting drug-release formulations (Peterson 2007). For this reason, we plan to carry out subgroup analyses of these factors. In addition, because pharmaceutical industry funding has been associated with positive trial results (Bekelman 2003; Riera 2017), the type of funding (i.e. with and without pharmaceutical industry funding) also merits a subgroup analysis.

Amphetamines have been blamed for causing 20 deaths among patients in Canada receiving these drugs for the treatment of ADHD, and these drugs were temporarily pulled from the market in that country (Kondro 2005). Amphetamines moreover can cause withdrawal effects (Phillips 2014), and they can be misused (Weyandt 2016). Therefore, we also aim to review the adverse effects of amphetamines, with a special emphasis on cardiovascular and psychiatric outcomes.

Finally, the change in diagnostic criteria with the introduction of DSM-5, which permits a diagnosis of ADHD in individuals with autism spectrum disorders, will allow investigation of the efficacy and safety of amphetamines in patients with this comorbidity.

OBJECTIVES

To examine the efficacy and safety of amphetamines for adults with ADHD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults (over 18 years of age) with ADHD, diagnosed by any standardised criteria (e.g. DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-10). The presence of comorbid disorders was not an exclusion criterion.

Types of interventions

Any amphetamine (including amphetamine, dextroamphetamine, lisdexamfetamine, or mixed amphetamine salts (MAS; Adderall)), given at any dose, compared with placebo or an active intervention(s).

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We did not exclude studies with additional interventions if these were provided to both study groups.

Types of outcome measures

Primary outcomes

1. Severity of ADHD symptoms, assessed by clinicians and patients using a standardised instrument (e.g. the ADHD Rating Scale-IV (ADHD-RS-IV; DuPaul 1998), Conners' Adult ADHD Rating Scale (CAARS; Conners 1999))

Secondary outcomes

1. Efficacy outcomes
   i) Clinical impression of severity at study end, measured by the Clinical Global Impression (CGI) - Severity (CGI-S) scale (Guy 1976)
   ii) Clinical impression of improvement at study end, assessed by the CGI-Improvement (CGI-I) scale (Guy 1976)
   iii) Proportion of participants achieving a reduction of at least 30% in severity of ADHD symptoms
   iv) Proportion of participants achieving a CGI-I score of 1 or 2
   v) Proportion of participants achieving a reduction of at least 30% in severity of ADHD symptoms and a CGI-I score of 1 or 2
   vi) Global functioning: social, occupational, and psychological functioning of adults with ADHD at study end, assessed by a standardised instrument
   vii) Depressive symptoms: severity of depressive symptoms at study completion, assessed by a standardised instrument
   viii) Anxiety: severity of anxiety symptoms at study completion, assessed by a standardised instrument
   ix) Retention: proportion of randomised participants that completed the study
2. Adverse events
   i) Proportion of participants withdrawn owing to any cardiovascular adverse event
   ii) Proportion of participants withdrawn owing to medication abuse
   iii) Proportion of participants withdrawn owing to any psychiatric adverse event
   iv) Proportion of participants withdrawn owing to any adverse event

Search methods for identification of studies

Electronic searches

We searched the following databases and trial registers in July 2016 and again in August 2017.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7) in the Cochrane Library, which contains the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register (searched 21 August 2017).
2. MEDLINE Ovid (1946 to August week 2 2017).
3. MEDLINE In-Process and Other Non-indexed Citations Ovid (searched 21 August 2017).
4. MEDLINE Epub Ahead of Print Ovid (searched 21 August 2017).
5. Embase Ovid (1974 to 2017 week 34).
6. PsycINFO Ovid (1967 to August week 2 2017).
7. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 to 23 August 2017).
8. Science Citation Index Web of Science (SCI; 1970 to 22 August 2017).
9. Social Science Citation Index Web of Science (SSCI; 1970 to 22 August 2017).
10. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to 22 August 2017).
11. Conference Proceedings Citation Index - Social Science and Humanities Web of Science (CPCI-SS&H; 1990 to 22 August 2017).
12. *Cochrane Database of Systematic Reviews* (CDSR; 2017, Issue 8), part of the Cochrane Library (searched 21 August 2017).
13. Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2), part of the Cochrane Library (final issue searched 29 July 2016).
14. Worldcat (www.worldcat.org; searched 23 August 2017).
15. Clinicaltrials.gov (clinicaltrials.gov; searched 23 August 2017).
16. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch; searched 23 August 2017).

We did not apply any language or date restrictions.

We have listed the search strategies for this update in Appendix 1, along with previous search strategies in Appendix 2.

Searching other resources

We contacted the corresponding authors of all included studies, experts in the field, and the pharmaceutical company, Shire, and we inspected the reference lists of retrieved studies and relevant reviews to identify any other published, unpublished, or ongoing studies. In addition, for each included study, we performed a citation search in Web of Science to identify any later studies that may have cited it.

Data collection and analysis

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Selection of studies

Having removed duplicates, two review authors (XC and RC) independently assessed the titles and abstracts of all remaining records yielded by the search strategy for eligibility, discarding those that were clearly irrelevant. Next, we acquired the full-text reports of those records deemed potentially eligible and assessed them against our inclusion criteria (see Criteria for considering studies for this review). When we identified unpublished trials, we contacted the study co-ordinators to request the data. We resolved disagreements by discussion, until reaching a consensus, or in consultation with a third review author (LB). We recorded our selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

Two review authors (XC and RC) independently inspected the full-text reports of included studies and extracted data onto a piloted data extraction sheet (Appendix 3). We resolved disagreements by discussion, until reaching a consensus, or in consultation with a third review author (LB).

Regarding our primary outcomes (severity of ADHD symptoms), we collected both change scores (the difference between ADHD symptom severity score at study end compared to baseline) and endpoint scores (ADHD symptom severity score at study end) but gave preference to change scores over endpoint scores. For all secondary outcomes (efficacy outcomes and adverse events), we collected endpoint scores.

We emailed study authors to request any missing data or information, when necessary. We also contacted the authors of all cross-over trials to obtain first period data on ADHD symptoms. We made a second approach if no answer was obtained by one month after the first email (see Dealing with missing data).

Two review authors (XC and RC) entered data into Review Manager 5 (RevMan 5) (Review Manager 2014).

Assessment of risk of bias in included studies

In accordance with the Cochrane 'Risk of bias' tool (Higgins 2017a), as well as the criteria set out in Appendix 4, two review authors (XC and RC) independently assessed the risk of bias in each included study as high, low, or unclear, for each of the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Review authors sought to resolve any differences by discussion, with MC adjudicating in cases for which this was not possible.

Measures of treatment effect

Continuous outcome data

We calculated the standardised mean difference (SMD) and 95% confidence intervals (CIs) because included studies used different scales to assess the severity of ADHD symptoms. We used Hedges' method for calculating SMD with individual study weights calculated as the inverse of the variance.

For both clinician- and patient-rated severity of ADHD symptoms, we entered data into RevMan using the generic inverse variance to combine data from parallel and cross-over studies in the manner recommended by Elbourne 2002 (see Unit of analysis issues section for additional details).

Dichotomous outcome data

We calculated the risk ratio (RR) and presented it with 95% CIs.

Unit of analysis issues

Cross-over trials

To combine parallel-group studies with cross-over studies, we calculated the correlation coefficient between active and control periods and used it to calculate effect sizes (Elbourne 2002). We used data from the first study period, when available, when we could not apply these recommendations.

We could calculate the correlation coefficient of the outcome score between active and control periods from only two studies (Taylor 2000; Taylor 2001). We applied the correlation coefficient to the other cross-over studies using the most conservative correlation coefficient (r = 0.44) in the main analysis (Taylor 2001); we used the least conservative one (r = 0.61) in a sensitivity analysis (Taylor 2000).

Multiple treatment groups

When several independent treatment groups were available (e.g. amphetamine + psychotherapy versus placebo + psychotherapy; amphetamine + fake psychotherapy versus placebo + fake psychotherapy), we included them as independent studies. In studies with multiple and correlated interventions (e.g. amphetamine 10 mg versus placebo; amphetamine 20 mg versus placebo), we combined the intervention groups into a single group and included them in the meta-analysis as a single comparison. For binary data, we summed sample sizes and numbers of participants with the event across groups. We combined continuous data using the formulae described in Section 7.7.3.8, "Combining groups", of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Dealing with missing data

We used the number of randomised participants as the denominator for dichotomous variables. For continuous data, we entered into Review Manager 2014 the sample size used in calculations of

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the mean and the standard deviation. We did not use any imputations to deal with missing data.

We emailed study authors to request missing data or information, when necessary. We also contacted Shire after the corresponding authors directed us to this pharmaceutical company to obtain the information requested (Castells 2009b [pers comm]). See Characteristics of included studies for data requested and subsequently provided.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing differences in study populations, interventions, and outcomes, and we evaluated methodological heterogeneity by comparing study designs.

We investigated statistical heterogeneity using tau², Chi² test, and the I² statistic, which determines the proportion of variability due to heterogeneity (I² from 0 to 40% = not important statistical heterogeneity; I² from 30% to 60% = moderate heterogeneity; I² from 50% to 90% = substantial heterogeneity; and I² from 75% to 100% = considerable heterogeneity (Deeks 2017)).

Assessment of reporting biases

We drew funnel plots to investigate any relationship between effect size and study precision (closely related to sample size) when we identified a sufficient number of studies (al least 10 studies) (Egger 1997).

Data synthesis

We used RevMan 5 to perform the analyses (Review Manager 2014).

We calculated weighted averages and 95% CIs using the inverse variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes. We pooled data using a random-effects model because we noted marked between-study heterogeneity as regards study design (studies with cross-over and parallel designs were included) and length of follow-up (from two to 20 weeks).

We examined the efficacy of amphetamines for reducing the severity of ADHD symptoms in adults by means of continuous outcome variables (using change scores, e.g. change in ADHD symptom severity score from baseline to study completion; and endpoint scores, e.g. ADHD symptom severity score at study completion) and binary ones (e.g. proportion of patients achieving a reduction of at least 30% in the severity of ADHD symptoms). The primary efficacy outcome (severity of ADHD symptoms) combined change scores and endpoint scores, but we prioritised change scores when both types of scores were available in the same study. We preferred change scores because they are more precise than endpoint scores, as long as they were adjusted for baseline severity. We analysed studies reporting response rates separately.

Summarising the quality of the evidence

Using GRADEpro (GRADEPro GDT 2015), we constructed a 'Summary of findings' table for the comparison of amphetamines versus placebo for ADHD in adults, for the following outcomes assessed post intervention: 'severity of ADHD symptoms' (primary outcome) assessed by clinicians and patients for each amphetamine; and retention in treatment (secondary outcome). Two review authors (XC and RC) assessed the quality of the evidence for each of these outcomes using the GRADE approach, resolving disagreements by discussion until reaching a consensus. GRADE offers a structured process for appraising the quality of evidence and developing recommendations based on the extent to which one can be confident that the estimates of effect are correct (Guyatt 2011a). The assessment may result in high-, moderate-, low- or very low-quality ratings based on evaluation of five categories: within-trial risk of bias, directness of evidence, heterogeneity of data, precision of effect estimates, and risk of publication bias (Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f).

Subgroup analysis and investigation of heterogeneity

Irrespective of whether we found statistical heterogeneity, we conducted the following subgroup analyses when we had sufficient studies (i.e. at least one study in each subgroup).

1. Comorbidities: the presence of a comorbidity (drug use disorder, major depressive disorder) versus no comorbidity.
2. Type of amphetamine (amphetamine, dextroamphetamine, lisdexamfetamine, or MAS).
3. Dose at study completion (equal to and above the median dose versus below the median dose). We performed this subgroup analysis separately for each type of amphetamine because no pharmacological equivalence was available for the three types of amphetamine that have been studied in adults with ADHD (dextroamphetamine, lisdexamfetamine, and MAS (which consists of a fixed-dose mixture of racaemic amphetamine aspartate monohydrate, racaemic amphetamine sulphate, dextroamphetamine saccharide, and dextroamphetamine sulphate)).
4. Type of drug-release formulation (immediate-release versus long-acting release).

We conducted subgroup analyses for the following outcomes only: severity of ADHD symptoms rated by clinicians and patients; retention in treatment; and proportion of participants withdrawn owing to any adverse events (because the number of studies measuring these outcomes was large enough to carry out these analyses). We calculated the pooled effect size (RR or SMD) for each subgroup. We investigated whether there were between-subgroup differences by means of the Chi² test, using a random-effects model.

We did not conduct our planned subgroup analysis for study funding (with versus without pharmaceutical industry funding)

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(Castells 2009a), as only was study was not funded by the pharmaceutical industry. See Differences between protocol and review.

Sensitivity analysis

We performed sensitivity analyses in which we restricted the meta-analysis of each outcome to those studies that had low risk of bias on that outcome. We had intended to restrict the analysis to studies that had low risk of bias in all domains (Castells 2009a), but this was not possible as no studies fulfilled this criterion. Instead, we used our assessments of incomplete outcome data and other potential sources of bias, whose scores showed between-study variability, and conducted sensitivity analyses that included only studies scoring low risk of bias on these specific domains.

We conducted three post hoc sensitivity analyses. First, we borrowed the correlation coefficient from Taylor 2000 to calculate the effect size of six cross-over studies (Dupaul 2012; Kay 2009; Martin 2014a/Martin 2014b; Spencer 2001; Wigal 2010) (see Unit of analysis issues). Second, we calculated the pooled risk difference for the outcomes of 'proportion of participants withdrawn owing to cardiovascular adverse events' and 'proportion of participants withdrawn owing to any adverse event', to include studies that had no events for these outcomes. Third, we excluded from the analysis one cross-over study (Spencer 2001), which had a carry-over effect, to determine wether the carry-over effect may have biased the results of this review.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

Our searches for this update yielded 3414 records, from which we identified and discarded 1391 duplicates. We screened titles and abstracts of the remaining 2023 records and retrieved 39 full-text reports for further examination. Of these, we excluded eight reports that did not meet our inclusion criteria (Criteria for considering studies for this review), and we identified eight secondary publications of previously included studies. We included 12 new studies (from 18 reports) and identified five ongoing studies, which, when combined with studies included in the previous version of the review (Castells 2011a), gives a total of 19 included studies (from 33 reports) and seven ongoing studies (from seven reports). See Figure 1.

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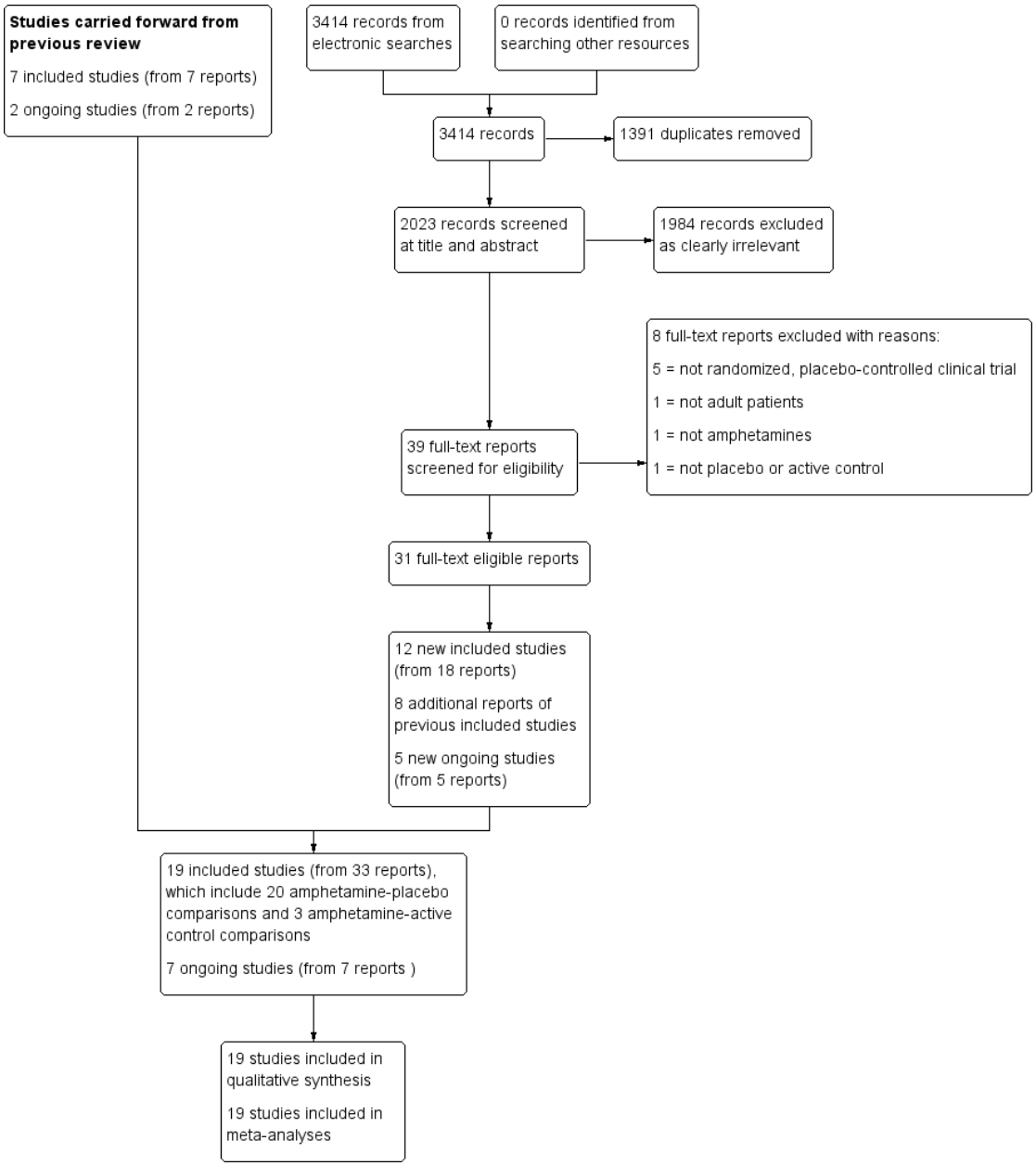
Figure 1. Flow diagram.



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Included studies

This review includes 19 studies (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Study design

Of the 19 studies included in this review, six used a cross-over design. All studies compared amphetamine versus placebo, and three studies also compared amphetamine versus an active intervention: guanfacine (Taylor 2001), modafinil (Taylor 2000), or paroxetine (Weiss 2006). One study investigated two types of amphetamines (lisdexamfetamine and MAS); thus we have included two drug versus placebo comparisons in the review (Martin 2014a/Martin 2014b).

Setting

Eighteen studies were conducted in the USA (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weisler 2017; Wigal 2010). One study was conducted in both Canada and the USA (Weiss 2006). Ten studies were multi-centre; that is, participants were enrolled and were followed up at more than one study site (Adler 2008; Adler 2013; Brams 2012; Frick 2017; Levin 2015; Spencer 2008; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Participants

The included studies randomised 2521 participants, mostly males (57.2%). Most participants were middle-aged Caucasians (mean age, 35.3 years) with a combined type of ADHD (78.8%). (For a detailed description of participant characteristics, see Table 1.) Sample sizes ranged from 17 participants in Taylor 2001 to 420 participants in Adler 2008.

Interventions

These studies investigated three types of amphetamines: dextroamphetamine in three studies (Taylor 2000; Taylor 2001; Weiss 2006); lisdexamfetamine in nine studies (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Kollins 2014; Martin 2014a; Waxmonsky 2014; Wigal 2010); and MAS in eight studies (Frick 2017; Kay 2009; Levin 2015; Martin 2014b; Spencer 2001; Spencer 2008; Weisler 2006; Weisler 2017).
Doses studied ranged from 10.2 mg/d in Taylor 2001 to 21.8 mg/d in Taylor 2000 for dextroamphetamine; from 30 mg/d in Adler 2008 and Dupaul 2012 to 70 mg/d in Adler 2008 and Dupaul 2012 for lisdexamfetamine; and from 12.5 mg/d in Weisler 2017 to 80 mg/d in Levin 2015 for MAS.

Duration

Duration of study interventions ranged from one week in Dupaul 2012 to 20 weeks in Weiss 2006, with a mean of 5.3 weeks (37.2 days). Only three studies were longer than eight weeks in duration (Adler 2013; Levin 2015; Weiss 2006).

Sponsorship

All but two studies reported their funding sources (Taylor 2000; Taylor 2001). With the exception of one study - Levin 2015 - all studies were funded by the pharmaceutical industry.

Excluded studies

In total, we excluded 17 studies (eight studies in this update and nine studies in the previous review) for the following reasons: 12 (70.6%) studies were not RCTs; three (17.6%) studies were not conducted in adults with ADHD (two studies were performed in children and one in individuals who had ADHD symptoms who did not qualify for the ADHD disorder), one (5.9%) study was not controlled with placebo or an active control, and one (5.9%) study did not investigate amphetamines. See Characteristics of excluded studies tables and Figure 1.

Ongoing studies

Seven clinical trials were still ongoing when we completed this update (NCT00202605; NCT00514202; NCT00928148; NCT01863459;
NCT02635035; NCT02803229; NCT03153488); two of these - NCT00514202 and NCT00202605 - were already identified in the previous version (Castells 2011a).
Four of these studies were completed (NCT00202605; NCT00514202; NCT00928148; NCT01863459), two are recruiting participants (NCT02635035; NCT02803229), and one is not yet recruiting (NCT03153488). Five studies investigated MAS (NCT00202605; NCT00514202; NCT00928148; NCT02803229; NCT03153488), and two studies investigated lisdexamfetamine (NCT01863459; NCT02635035). Four studies have a cross-over design (NCT00202605; NCT00928148;

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NCT01863459; NCT02635035), and three studies have a parallel design (NCT00514202; NCT02803229; NCT03153488). Three studies included patients with ADHD and comorbid disorders (NCT00514202; NCT01863459; NCT02803229). See Characteristics of ongoing studies.

Risk of bias in included studies

We have provided a comprehensive description of the risk of bias for each study in the 'Risk of bias' tables beneath the Characteristics of included studies tables. We have summarised this information in Figure 2.

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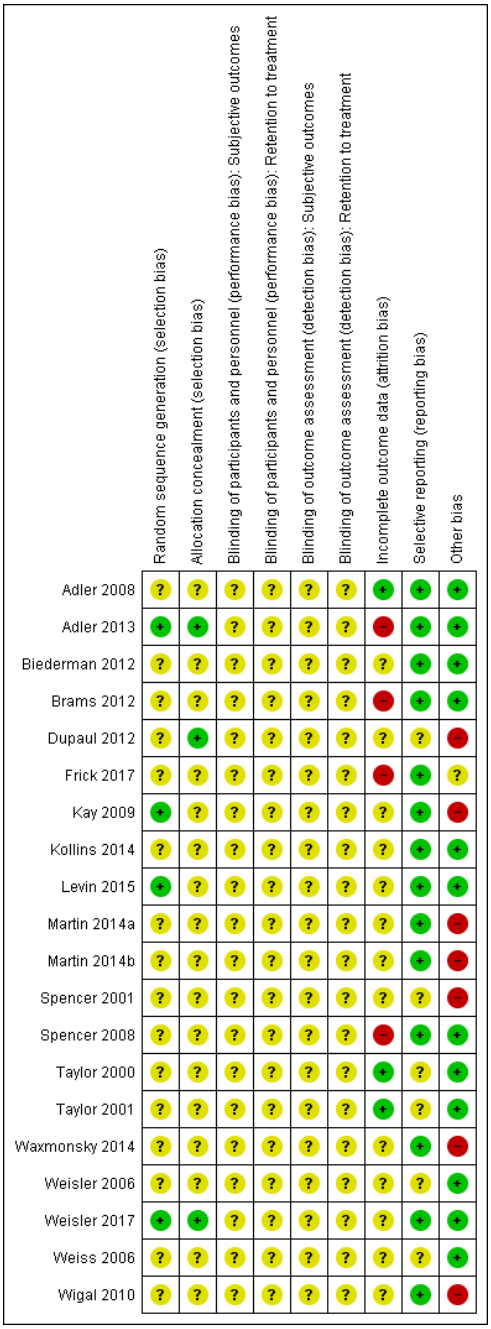
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.Note: scores for blinding of participants, personnel, and outcome assessors refer to amphetamines vs placebo only comparisons; scores on all remaining domains refer to amphetamines vs placebo, guanfacine, modafinil, or paroxetine.



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Allocation

Sequence generation

Four studies reported on how the random sequence was generated, and so we considered their risk of bias to be low (Adler 2013; Kay 2009; Levin 2015; Weisler 2017). The 16 remaining studies did not report on how the random sequence was generated, and so we judged them to be at unclear risk of bias (Adler 2008; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kollins 2014; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weiss 2006; Wigal 2010).

Allocation concealment

Three studies reported on their method of allocation concealment, and so we considered their risk of bias to be low (Adler 2013; Dupaul 2012; Weisler 2017). The 17 remaining studies did not report on their method of allocation concealment, and so we judged them to be at unclear risk of bias (Adler 2008; Biederman 2012; Brams 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weiss 2006; Wigal 2010).

Blinding

Blinding of participants and personnel (performance bias)

Blinding of participants and personnel was intended in all included studies (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010). Nevertheless, we deemed all studies to be unclear risk of performance bias, given that amphetamines have powerful subjective effects that may reveal the assigned treatment (Childs 2009; Johanson 1980; Makris 2004; Makris 2007; Wachtel 1992).

Blinding of outcome assessment (detection bias)

Blinding of outcome assessment was intended in all included studies (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2001; Spencer 2008; Taylor 2000; Taylor 2001; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010). Nevertheless, we deemed all studies to be unclear risk of detection bias, given that amphetamines have powerful subjective effects that may reveal the assigned treatment (Childs 2009; Johanson 1980; Makris 2004; Makris 2007; Wachtel 1992).

Incomplete outcome data

Study outcomes can be influenced by attrition because reasons for dropping out from the study may differ between active intervention and placebo groups. This selective attrition makes intervention groups that were similar at baseline different at the end of the study. This appears to be the case in studies investigating the efficacy of amphetamines for adults with ADHD. As discussed later, the proportion of participants dropping out owing to AEs was higher amongst those receiving amphetamines than placebo, suggesting that attrition was somehow related to the experimental intervention. This selective attrition can lead to bias. This is particularly true for studies with a higher dropout rate (Adler 2013), and for those with statistically significant differences in the number of dropouts between study groups (Brams 2012; Frick 2017; Spencer 2008); we rated these studies at high risk of attrition bias. In such an instance, no statistical method of dealing with missing data appears to guarantee unbiased results. Conversely, this type of bias seems unlikely amongst those studies for which attrition was low (Adler 2008; Taylor 2000; Taylor 2001); we considered these studies to be at low risk of attrition bias. For the remaining 12 studies, we judged the risk of attrition bias to be unclear because attrition was moderate but imputation methods for missing data were applied, or attrition was low but missing data were not imputed (Biederman 2012; Dupaul 2012; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2001; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Selective reporting

For 13 studies, the protocol was available and outcomes stated in the protocol were reported in the article (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a/Martin 2014b; Spencer 2008; Waxmonsky 2014; Weisler 2017; Wigal 2010). We considered these studies to be at low risk of reporting bias. For the six remaining studies, the study protocol was not available and thus we considered them to be at unclear risk of reporting bias (Dupaul 2012; Spencer 2001; Taylor 2000; Taylor 2001; Weisler 2006; Weiss 2006).

Other potential sources of bias

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We considered seven studies to be at high risk of other bias (Dupaul 2012; Kay 2009; Martin 2014a; Martin 2014b; Spencer 2001; Waxmonsky 2014; Wigal 2010), mainly because they had a cross-over design with no washout phase, and thus the possibility of a carry-over effect could not be ruled out. Indeed, in one of these studies the carry-over effect was evident (Spencer 2001). The carry-over effect can yield an underestimation of the effect of the intervention and can bias the result towards the null for both effectiveness and AE outcomes. For one study - Frick 2017 - we judged the risk of other bias to be unclear because there was a long period of time between performance of the study and publication of the main results and, in addition, secondary results were published before the main results were published. For the 12 remaining studies, groups were balanced at baseline and no other potential source of bias was found; thus we considered them to be at low risk of other bias (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Kollins 2014; Levin 2015; Spencer 2008; Taylor 2000; Taylor 2001; Weisler 2006; Weisler 2017; Weiss 2006).

Summary

We did not rate any study as having low risk of bias overall because we considered all of them to be at unclear or high risk of bias in at least one domain of the Cochrane 'Risk of bias' tool. For all studies, we considered the risk of performance and detection bias to be unclear because it is likely that participants or clinicians would have detected the medication, given the powerful behavioural effects of amphetamines. This bias is unlikely to occur if amphetamines are compared with other psychostimulants such as modafinil or methylphenidate. Furthermore, attrition bias is likely in several studies, and the possibility of a carry-over effect could not be ruled out in studies using a cross-over design.

Effects of interventions

See: **Summary of findings for the main comparison** Amphetamines versus placebo for attention deficit hyperactivity disorder (ADHD) in adults

Amphetamines versus placebo

We were able to perform meta-analyses for most outcomes, given the high availability of data: 'ADHD symptom severity: clinician' (68.4%), 'Retention in treatment' (84.2%), and 'Proportion of participants withdrawn owing to any adverse event' (84.2%). We present the results for each outcome below, along with results for the outcomes of 'severity of ADHD symptoms' assessed by clinicians and patients for each amphetamine, and we present results for 'retention to treatment' in Summary of findings for the main comparison.

Primary outcomes: severity of ADHD symptoms

We found evidence to suggest that amphetamines are more efficacious than placebo in reducing the severity of ADHD symptoms whether assessed by clinicians (standardised mean difference (SMD) −0.90, 95% confidence interval (CI) −1.04 to −0.75; 13 studies, 2028 participants; Analysis 1.1; Figure 3; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Frick 2017; Kollins 2014; Levin 2015; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2017; Weiss 2006; Wigal 2010) or by patients (SMD −0.51, 95% CI −0.75 to −0.28; six studies, 120 participants; Analysis 1.2; Dupaul 2012; Kollins 2014; Martin 2014a; Martin 2014b; Taylor 2000; Taylor 2001). Statistical heterogeneity for severity of ADHD symptoms was moderate when rated by clinicians (I^2 = 47%) and was low (I^2 = 13%) when rated by patients. We drew a funnel plot for clinician-rated efficacy and detected no asymmetry (Figure 4).

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Figure 3. Forest plot of comparison: 1 Amphetamines vs placebo for ADHD in adults, outcome: 1.1 Severity of ADHD symptoms: clinician rated.

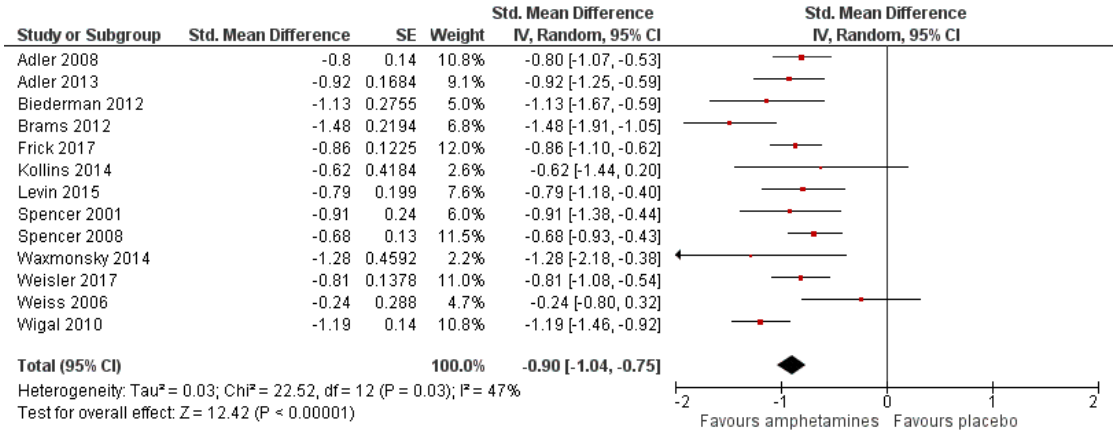
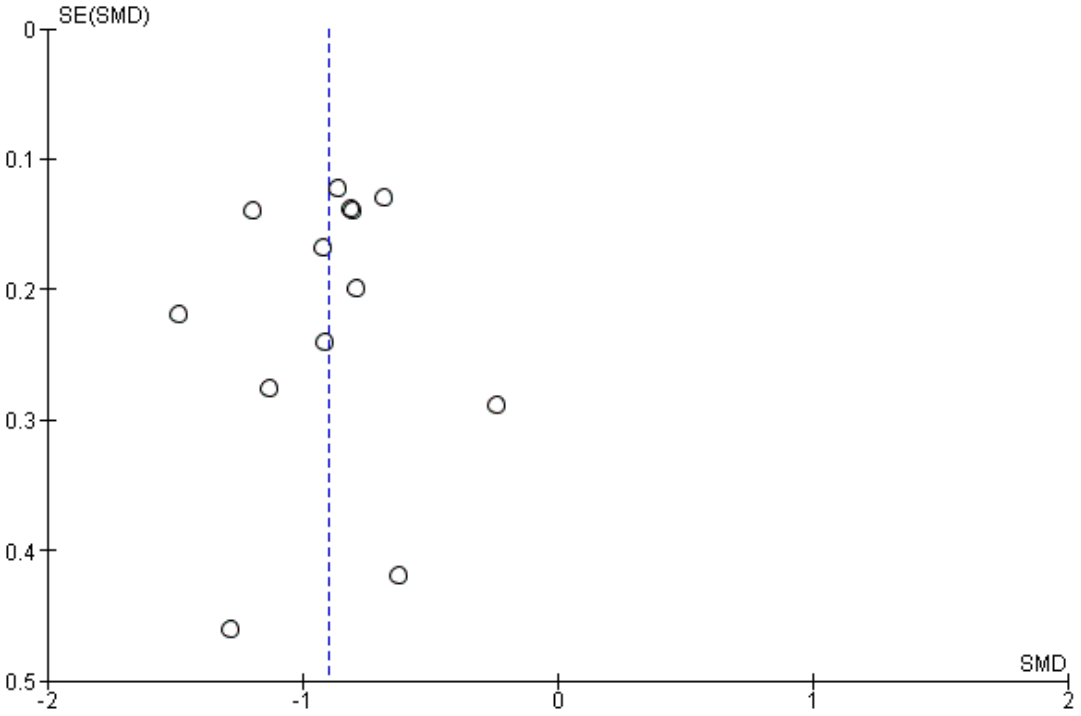


Figure 4. Funnel plot of comparison: 1 Amphetamines vs placebo for ADHD in adults, outcome: 1.1 Severity of ADHD symptoms: clinician rated.



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Secondary outcomes

Efficacy outcomes

We found evidence that amphetamines are more efficacious than placebo in reducing the severity of ADHD symptoms, irrespective of the efficacy definition used.

1. Clinical impression of severity at study end (SMD −1.09, 95% CI −1.57 to −0.61; two studies, 78 participants; Analysis 1.3; Spencer 2001; Waxmonsky 2014).
2. Clinical impression of improvement at study end (one study, 263 participants; Analysis 1.4; Weisler 2017).
3. Proportion of participants achieving a reduction of at least 30% in the severity of ADHD symptoms (risk ratio (RR) 1.52, 95% CI 1.19 to 1.95; two studies, 381 participants; Analysis 1.5; Levin 2015; Weisler 2006).
4. Proportion of participants achieving a CGI-I score of 1 or 2 (RR 2.47, 95% CI 2.10 to 2.90; eight studies, 1707 participants; Analysis 1.6; Adler 2008; Adler 2013; Frick 2017; Levin 2015; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weiss 2006).
5. Proportion of participants achieving a reduction of at least 30% in the severity of ADHD symptoms and a CGI-I score of 1 or 2 in another study (one study, 61 participants; Analysis 1.7; Biederman 2012).

We found no statistical heterogeneity for any of these outcomes.

We conducted a meta-analysis of two studies with 110 participants (Biederman 2012; Weiss 2006), which revealed no differences between the groups given amphetamines and those given placebo in global functioning (SMD 0.54, 95% CI −0.34 to 1.42; Analysis 1.8), depressive symptoms (SMD 0.16, 95% CI −0.22 to 0.53; Analysis 1.9), or anxiety symptoms (SMD 0.13, 95% CI −0.24 to 0.51; Analysis 1.10). Nevertheless, few studies provided data on these outcomes in a way that was suitable for meta-analysis.

In another meta-analysis of 17 studies with 2323 participants (Adler 2008; Adler 2013; Biederman 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010), we found no evidence to suggest that amphetamines improve retention in treatment (RR 1.06, 95% CI 0.99 to 1.13; low-quality evidence; Analysis 1.11; Figure 5). This latter analysis showed moderate statistical heterogeneity (I^2 = 40%), but we detected no asymmetry in the funnel plot (not shown).

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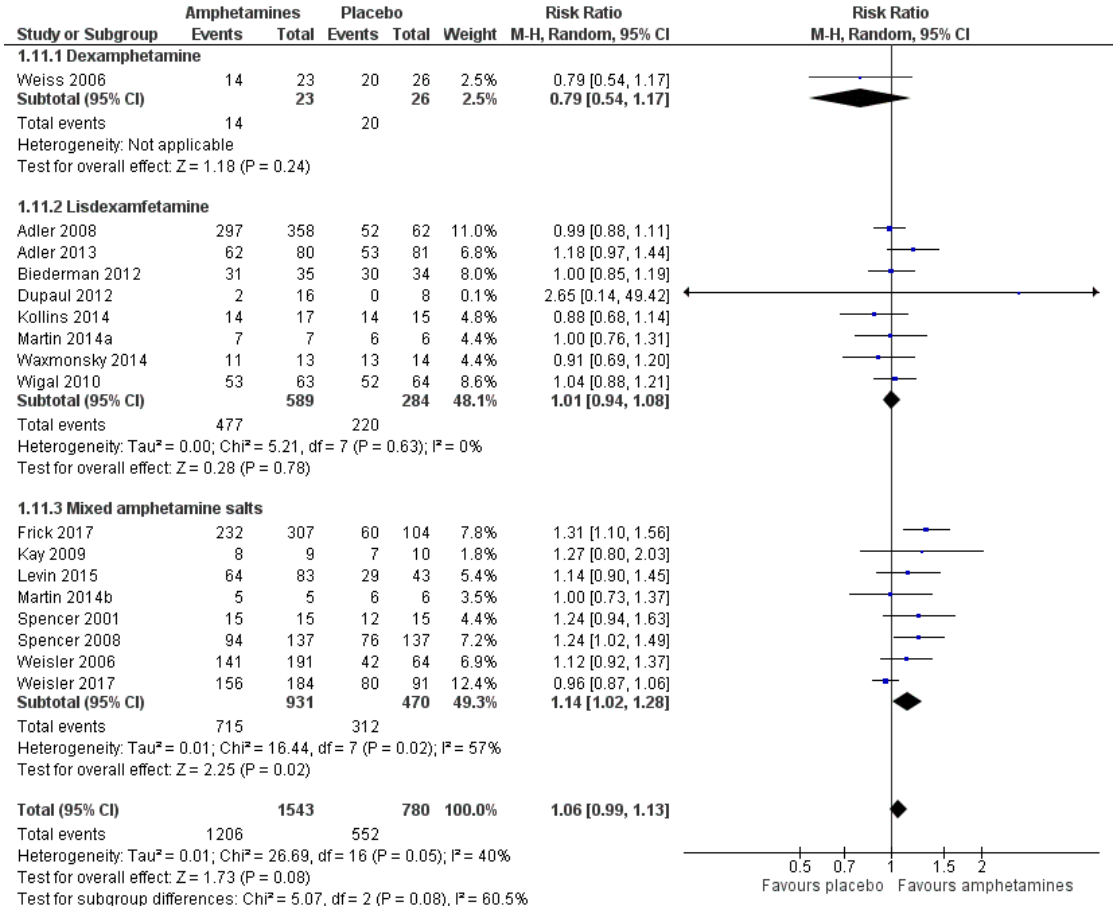
Figure 5. Forest plot of comparison: 1 Amphetamines vs placebo for ADHD in adults, outcome: 1.11 Retention in treatment.



Adverse events

A meta-analysis of three studies with 699 participants showed that a higher proportion of participants in the amphetamine group than in the placebo group dropped out owing to cardiovascular adverse events. However, this difference was not statistically significant (RR 2.18, 95% CI 0.39 to 12.04; Analysis 1.12; Adler 2008; Dupaul 2012; Weisler 2006).

We conducted a meta-analysis of 17 studies with 2409 participants and found that the proportion of participants who dropped out owing to any adverse event was higher in the amphetamine group than in the placebo group (RR 2.69, 95% CI 1.63 to 4.42; Analysis 1.13; Figure 6) (Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010). However, it must be noted that the proportion of participants who were withdrawn owing to any adverse event was low, even in the amphetamines arm (7.6%).

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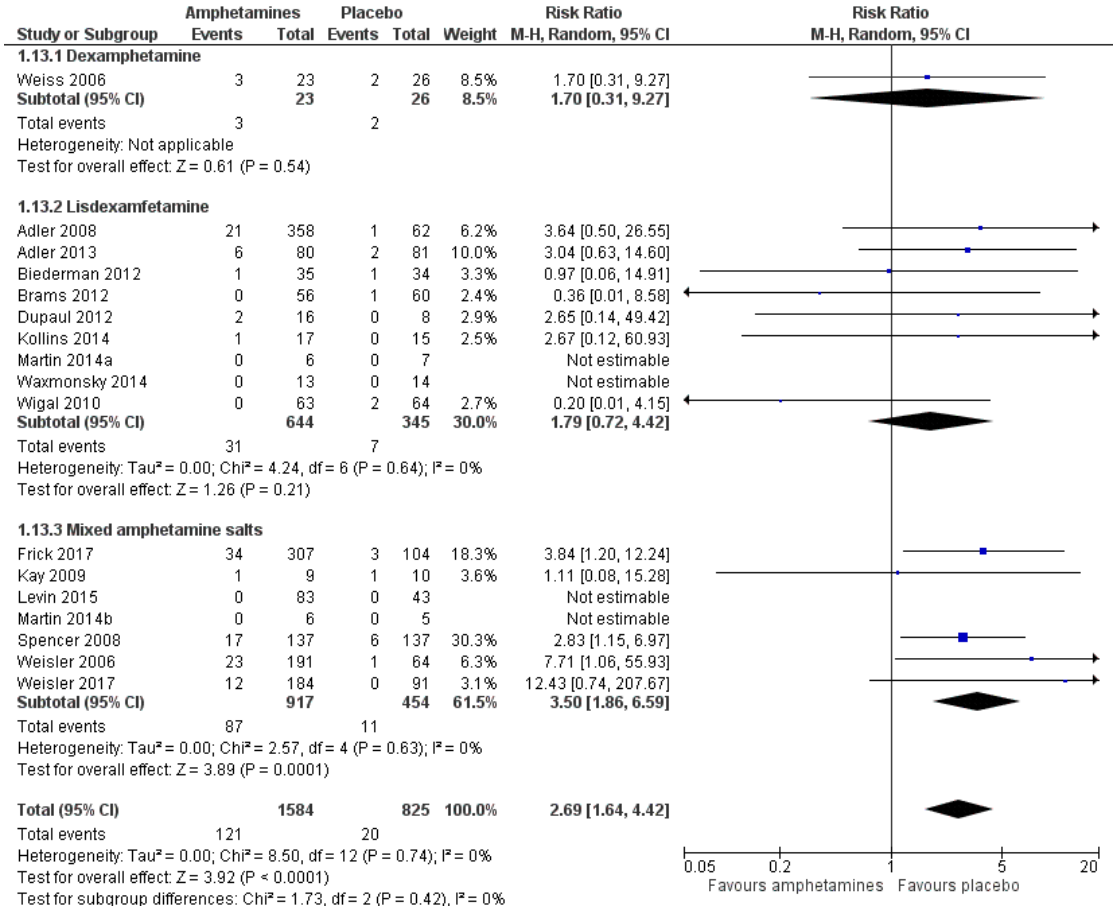
Figure 6. Forest plot of comparison: 1 Amphetamines vs placebo for ADHD in adults, outcome: 1.13 Proportion of participants withdrawn owing to any adverse event.



We found no statistical heterogeneity for any adverse events.

No study reported data on the remaining two outcomes: 'proportion of participants withdrawn owing to medication abuse' and 'proportion of participants withdrawn owing to any psychiatric adverse event'.

Subgroup analyses

Comorbidity

We found no evidence to suggest that comorbidity influenced the effects of amphetamines on:

1. severity of ADHD symptoms assessed by clinicians (SMD −0.90, 95% CI −1.04 to −0.75; 13 studies, 2028 participants; Analysis 2.1; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Frick 2017; Kollins 2014; Levin 2015; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2017; Weiss 2006; Wigal 2010);
2. severity of ADHD symptoms assessed by participants (SMD −0.51, 95% CI −0.75 to −0.28; six studies, 120 participants; Analysis 2.2; Dupaul 2012; Kollins 2014; Martin 2014a; Martin 2014b; Taylor 2000; Taylor 2001);
3. retention in treatment (RR 1.06, 95% CI 0.99 to 1.13; 17 studies, 2323 participants; Analysis 2.3; Adler 2008; Adler 2013; Biederman 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010); or
4. proportion of participants withdrawn owing to any adverse event (RR 2.69, 95% CI 1.63 to 4.42; 17 studies, 2409 participants; Analysis 2.4; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins

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2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Types of amphetamines

Included studies assessed the effects of three amphetamines: dexamphetamine, lisdexamfetamine, and MAS. We found differences between these three types of amphetamines in the reduction in severity of ADHD symptoms assessed by clinicians (Analysis 3.1): both lisdexamfetamine and MAS were more efficacious than placebo in reducing the severity of ADHD symptoms (lisdexamfetamine: SMD −1.06, 95% CI −1.26 to −0.85; seven studies, 896 participants; Figure 3; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Kollins 2014; Waxmonsky 2014; Wigal 2010; MAS: SMD −0.80, 95% CI −0.93 to −0.66; five studies, 1083 participants; Figure 3; Frick 2017; Levin 2015; Spencer 2001; Spencer 2008; Weisler 2006), but not dexamphetamine (SMD −0.24, 95% CI −0.80 to 0.32; one study, 49 participants; Figure 3; Weiss 2006).

We also found evidence to suggest that both dexamphetamine and lisdexamfetamine are more efficacious than placebo in reducing the severity of ADHD symptoms as assessed by participants (dexamphetamine: SMD −0.77, 95% CI −1.14 to −0.40; two studies, 35 participants; Taylor 2000; Taylor 2001; lisdexamfetamine: SMD −0.33, 95% CI −0.65 to −0.01; three studies, 67 participants; Dupaul 2012; Kollins 2014; Martin 2014a), but not MAS (SMD −0.45, 95% CI −1.02 to 0.12; one study, 18 participants; Martin 2014b). See Analysis 3.2.

We found no between-group differences in retention in treatment (RR 1.06, 95% CI 0.99 to 1.13; 17 studies, 2323 participants; Analysis 3.3; Adler 2008; Adler 2013; Biederman 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010), or in the proportion of participants withdrawn owing to adverse events (RR 2.69, 95% CI 1.63 to 4.42; 17 studies, 2409 participants; Analysis 3.4; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Dose at study completion

The amphetamine maintenance dose was available for all but two studies (Biederman 2012; Weiss 2006). We studied the influence of dose by splitting available comparisons into two groups (lower versus higher doses). The cutoff for delimiting low and high doses was 16 mg/d for dexamphetamine, 53.4 mg/d for lisdexamfetamine, and 50 mg/d for MAS. Four studies compared three doses of amphetamines versus placebo (Adler 2008; Dupaul 2012; Frick 2017; Weisler 2006), thus providing three amphetamine versus placebo comparisons. We combined two of these three comparisons into the same subgroup, thereby leaving two amphetamine (higher and lower doses) versus placebo comparisons (see Unit of analysis issues for the explanation on methods used to combine multiple and correlated interventions). Two studies - Levin 2015 and Weisler 2017 - compared two amphetamine doses versus placebo, which we combined into the same subgroup because both were above or below the median dose (Levin 2015; Weisler 2017).

We found no evidence that dose influenced the effects of:

1. dexamphetamine on severity of ADHD symptoms as assessed by participants (SMD −0.77, 95% CI −1.14 to −0.40; two studies, 35 participants; Analysis 4.1; Taylor 2000; Taylor 2001);
2. lisdexamfetamine on severity of ADHD symptoms as assessed by clinicians (SMD −1.02, 95% CI −1.22 to −0.82; six studies, 885 participants; Analysis 5.1; Adler 2008; Adler 2013; Brams 2012; Kollins 2014; Waxmonsky 2014; Wigal 2010), or as assessed by participants (SMD −0.35, 95% CI −0.61 to −0.10; three studies, 67 participants; Analysis 5.2; Dupaul 2012; Kollins 2014; Martin 2014a); retention in treatment (RR 1.00, 95% CI 0.93 to 1.08; five studies, 712 participants; Analysis 5.3; Adler 2008; Adler 2013; Dupaul 2012; Kollins 2014; Martin 2014a); or the proportion of participants withdrawn owing to any adverse event (RR 2.72, 95% CI 1.09 to 6.75; six studies, 828 participants; Analysis 5.4; Adler 2008; Adler 2013; Brams 2012; Dupaul 2012; Kollins 2014; Martin 2014a); and
3. MAS on severity of ADHD symptoms as assessed by clinicians (SMD −0.81, 95% CI −0.94 to −0.69; five studies, 1083 participants; Analysis 6.1; Frick 2017; Levin 2015; Spencer 2001; Spencer 2008; Weisler 2017); retention in treatment (RR 1.16, 95% CI 1.05 to 1.28; eight studies, 1569 participants; Analysis 6.2; Frick 2017; Kay 2009; Levin 2015; Martin 2014b; Spencer 2001; Spencer 2008; Weisler 2006; Weisler 2017); or the proportion of participants withdrawn owing to any adverse event (RR 3.73, 95% CI 2.16 to 6.44; seven studies, 1539 participants; Analysis 6.3; Frick 2017; Kay 2009; Levin 2015; Martin 2014b; Spencer 2008; Weisler 2006; Weisler 2017).

Type of drug-release formulation

We found no evidence to suggest that the type of drug-release formulation influences the effects of amphetamines on:

1. severity of ADHD symptoms as assessed by clinicians (SMD −0.90, 95% CI −1.04 to −0.75; 13 studies, 2028 participants; Analysis 7.1; Adler 2008; Adler 2013; Biederman 2012; Brams 2012; Frick 2017; Kollins 2014; Levin 2015; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weiss 2006; Wigal 2010);
2. severity of ADHD symptoms as assessed by participants (SMD −0.51, 95% CI −0.75 to −0.27; six studies, 120 participants; Analysis 7.2; Dupaul 2012; Kollins 2014; Martin

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2014a; Martin 2014b; Taylor 2000; Taylor 2001); or

3. retention in treatment (RR 1.06, 95% CI 0.99 to 1.13; 17 studies, 2323 participants; Analysis 7.3; Adler 2008; Adler 2013; Biederman 2012; Dupaul 2012; Frick 2017; Kay 2009; Kollins 2014; Levin 2015; Martin 2014a; Martin 2014b; Spencer 2001; Spencer 2008; Waxmonsky 2014; Weisler 2006; Weisler 2017; Weiss 2006; Wigal 2010).

Study funding

Twelve studies were funded by the pharmaceutical industry; only one was a non-commercial study. We decided post hoc not to conduct a subgroup analysis of study funding given the difference in the number of studies included within each subgroup, which could compromise the validity of these analyses.

Sensitivity analyses

We performed sensitivity analyses by limiting analyses to those studies scoring low risk of bias on two specific domains of the Cochrane 'Risk of bias' tool, namely, incomplete outcome data and other potential sources of bias. Findings from these analyses were similar to those of the primary analyses (incomplete outcome data: Analysis 8.1; Analysis 8.2; other potential sources of bias: Analysis 9.1; Analysis 9.2; Analysis 9.3).

We ran another sensitivity analysis by changing the statistical model from a random-effects model, which we used to pool data in the main analysis, to a fixed-effect model. We observed similar results for efficacy outcomes (Analysis 10.1; Analysis 10.2; Analysis 10.3; Analysis 1.4; Analysis 1.5; Analysis 10.6; Analysis 10.7; Analysis 10.8; Analysis 10.9; Analysis 10.10), with the exception of retention in treatment, which was higher for amphetamines than for placebo (Analysis 10.11: RR 1.10, 95% CI 1.04 to 1.16; 17 studies, 2323 participants). We observed similar results for adverse events when using the fixed-effect model (Analysis 10.12; Analysis 10.13).

We also conducted three post hoc sensitivity analyses.

1. We repeated the analysis of the severity of ADHD symptoms as rated by clinicians and participants after calculating the effect size of four studies (Dupaul 2012; Martin 2014a/Martin 2014b; Spencer 2001; Wigal 2010) using the least conservative correlation coefficient (see Unit of analysis issues). Results of these analyses (clinician rated: SMD −0.90, 95% CI −1.05 to −0.76; 13 studies, 2028 participants; Analysis 11.1; participant rated: SMD −0.47, 95% CI −0.69 to −0.25; six studies, 120 participants; Analysis 11.2) were comparable with results of the original analyses (clinician rated: SMD −0.90, 95% CI −1.04 to −0.75; 13 studies, 2028 participants; Analysis 1.1; patient rated: SMD −0.51, 95% CI −0.75 to −0.28; six studies, 120 participants; Analysis 1.2).
2. In the second analysis, we re-analysed the outcomes of 'proportion of participants withdrawn owing to any cardiovascular adverse event' and 'proportion of participants withdrawn owing to any adverse event', calculating the risk difference (RD) (Analysis 12.1: RD 0.02, 95% CI −0.00 to 0.04; three studies, 699 participants; Analysis 12.2: RD 0.04, 95% CI 0.01 to 0.06; 17 studies, 2409 participants, respectively). This yielded similar findings to the previous analyses (Analysis 1.12: RR 2.18, 95% CI 0.39 to 12.04; three studies, 699 participants; Analysis 1.13: RR 2.69, 95% CI 1.64 to 4.42; 17 studies, 2409 participants, respectively).
3. In the third analysis, we removed one study (Spencer 2001), which was showing a carry-over effect from the analysis on severity of ADHD symptoms (Analysis 13.1: SMD −0.90, 95% CI −1.05 to −0.74; 12 studies, 1998 participants), and obtained similar results to the primary analysis (Analysis 1.1: SMD −0.90, 95% CI −1.04 to −0.75; 13 studies, 2028 participants), suggesting that inclusion of this study did not bias the results of this review.

Amphetamines versus guanfacine

Only one study (17 participants) compared the efficacy of amphetamines versus guanfacine (Taylor 2001).

Primary outcomes: severity of ADHD symptoms

Taylor 2001 found no evidence to suggest that amphetamines are superior to guanfacine in reducing the severity of ADHD symptoms as rated by participants (Analysis 14.1).

Secondary outcomes

Taylor 2001 did not provide data on any of our secondary outcomes.

Amphetamines versus modafinil

Only one study (22 participants) compared the efficacy of amphetamines versus modafinil (Taylor 2000).

Primary outcomes: severity of ADHD symptoms

Taylor 2000 found no evidence to suggest that amphetamines are superior to modafinil in reducing the severity of ADHD symptoms as rated by participants (Analysis 15.1).

Secondary outcomes

Taylor 2000 did not provide data on any of our secondary outcomes.

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Amphetamines versus paroxetine

Only one study (98 participants) compared the efficacy of amphetamines versus paroxetine (Weiss 2006).

Primary outcomes: severity of ADHD symptoms

Weiss 2006 found no evidence to suggest that amphetamines are superior to paroxetine in reducing the severity of ADHD symptoms as rated by clinicians (Analysis 16.1).

Secondary outcomes

Efficacy outcomes

Weiss 2006 found evidence indicating that amphetamines are more efficacious than paroxetine in increasing the proportion of participants achieving a CGI-I score of 1 or 2 (Analysis 16.2), but are not more efficacious than paroxetine in improving global functioning (Analysis 16.3), reducing symptoms of depression (Analysis 16.4) or anxiety (Analysis 16.5), or improving retention in treatment (Analysis 16.6).

Adverse events

Weiss 2006 found no evidence that amphetamines are more efficacious than paroxetine in reducing the proportion of participants withdrawn owing to any adverse event (Analysis 16.7).

DISCUSSION

Summary of main results

Amphetamines showed mixed results in the treatment of adults with attention deficit hyperactivity disorder (ADHD). We found low- to very low-quality evidence suggesting that amphetamines were more efficacious than placebo in reducing the severity of ADHD symptoms, irrespective of the rater, and low-quality evidence that they did not improve retention in treatment. Furthermore, amphetamines were associated with increased risk of dropping out owing to adverse events. Amphetamines were not effective in improving depressive and anxiety symptoms nor global functioning.

This review found that amphetamines reduced the severity of ADHD symptoms in adults in the short term. This finding was consistent across all analyses that were conducted using different efficacy definitions and statistical models. Furthermore, in most analyses, effect sizes of amphetamines for improving ADHD symptoms were moderate to high according to conventional cut-offs (Cohen 1988).

The included studies were of short duration, lasting an average of only 5.3 weeks. This is notable for three reasons. First, ADHD is a chronic disorder, and pharmacological treatment is usually administered over long periods of time. Second, because severity tends to lessen with age (Biederman 2000; Faraone 2006; Hill 1996), the possibility that the efficacy of amphetamines in adult ADHD is less after long-term amphetamine treatment cannot be ruled out and should be studied through clinical trials with a longer follow-up period. Third, some reports suggest that the efficacy of drugs used to treat ADHD tends to decrease progressively over time (Cunill 2016; MTA 2004; Riera 2017). Therefore, given that most included studies were of short duration, it is possible that effect sizes of amphetamines are smaller over the long term.

As a group, amphetamines did not improve retention in treatment. Retention can be interpreted as a risk-benefit outcome because it reflects the combined evaluation of efficacy and safety (Castells 2013; Cunill 2013; Schhneider 2006; Stroup 2003). This result cannot be considered a positive one, as it is always desirable for any intervention to show a lower discontinuation rate than placebo, suggesting that the efficacy of the medication outweighs its side effects.

We found between-study variability in relation to the severity of ADHD symptoms as assessed by clinicians. This resulted in moderate statistical heterogeneity. We investigated the source of this heterogeneity via four subgroup analyses (comorbidities, types of amphetamines, dose at study completion, and type of drug-release formulation). Even though we found an effect for the type of amphetamine on the severity of ADHD symptoms, with lisdexamfetamine and MAS showing larger effect sizes than dexamphetamine, this factor did not entirely explain the between-study variability, as within-subgroup statistical heterogeneity remained evident. We also found moderate statistical heterogeneity for 'retention to treatment', but no subgroup analyses could control for such heterogeneity, which is likely to be explained by other covariates or a combination of them.

As stated above, we found that the type of amphetamine influenced clinician-rated ADHD efficacy: although both lisdexamfetamine and MAS reduced the severity of ADHD symptoms compared to placebo, dexamphetamine did not. The type of amphetamine did not influence participant-rated ADHD efficacy, retention to treatment, or adverse events. This result, along with the fact that dextroamphetamine has been infrequently studied, provides indirect and low-quality evidence preferring lisdexamfetamine and MAS over dextroamphetamine.

Studies have investigated a wide range of doses, and higher and lower doses of amphetamine have shown similar results. This finding is consistent with that of clinical trials that have investigated the efficacy of multiple amphetamine doses and found no differences between treatment arms (Adler 2008; Weisler 2006). Methylphenidate given at a wide range of doses has also been investigated, and findings regarding its dose-response effects have been contradictory: some studies suggested a positive relationship

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(Castells 2011b; Faraone 2004; Medori 2008), and others found no association with dose (Koesters 2008; Spencer 2007).

Amphetamines have a short half-life and must be administered two or three times a day. To facilitate treatment compliance, sustained-release formulations have been developed. This systematic review showed that amphetamines delivered via immediate-release and slow-release formulations had similar efficacy and tolerability. This is relevant, as long-acting formulations have been found to be less efficacious than short-acting ones (Peterson 2007).

Few studies included participants with comorbid disorders, which contrasts with the high prevalence of other psychiatric conditions diagnosed in patients with ADHD (Kessler 2006). The presence of comorbid disorders did not modify efficacy, retention to treatment, nor adverse events. This finding is consistent with those of a recent study that did not find comorbidity to modify the effects of pharmacological treatment in adults with ADHD (Cunill 2016).

We did not assess the effects of study sponsorship on efficacy, retention to treatment, or adverse events, because with the exception of one study, all were sponsored by the pharmaceutical industry. Other studies have shown that studies with a commercial sponsor report more favourable outcomes than are reported by independent studies (Lundh 2017; Riera 2017).

Failure to identify an impact of amphetamines on depressive and anxiety symptoms could be a consequence of the strict inclusion criteria adopted by most included studies, which excluded patients with major depressive or bipolar disorders. Baseline depression and anxiety scores therefore were low, leaving little room for improvement. Another possible interpretation is that the effects of amphetamines on ADHD symptoms are independent of effects on mood and anxiety. The number of studies included in these analyses was low, limiting our ability to draw conclusions.

Amphetamines have been compared with only three drugs (guanfacine, modafinil, and paroxetine) in three small clinical trials. Therefore, it is not surprising that no differences have been found for most outcomes.

Overall completeness and applicability of evidence

The overall completeness and applicability of evidence related to the efficacy and safety of amphetamines are limited by two factors. First, the dearth of data on patients with ADHD with comorbid disorders such as substance abuse or major depressive disorder. This is particularly notable given the high prevalence of comorbid psychiatric disorders in patients with ADHD (Biederman 2006; Levin 1998; Van Emmerik-van Oortmerssen 2012; Young 2005), which is expected to increase further with the use of DSM-5, as it permits a diagnosis of ADHD in patients with autism spectrum disorders. Second, the short duration of studies, which contrasts with the chronic course and long-term treatment of the disorder. However, strengths must also be acknowledged. This review includes a systematic and exhaustive search that permitted us to identify all amphetamine trials performed in adults with ADHD. In addition, we were able to obtain a large quantity of missing data of interest from the trial authors of a number of studies included in this review.

Quality of the evidence

We did not find any study that was free of bias. Most articles reported neither on how the random sequence was generated nor how it was concealed. Therefore, we were not able to differentiate between reporting problems and study bias. However, even if these processes had been performed correctly, no study would have been rated as free of bias because amphetamines have intense behavioural effects, and participants and raters may have detected the administered study medication. This detection may have caused a blinding failure, which might have exaggerated the efficacy of the intervention (Schultz 1995); this type of bias is less likely to occur when amphetamines are compared to other psychostimulants such as modafinil (Taylor 2000). However, no study assessed whether blinding had failed, and the fact that all studies were scored at unclear risk of bias on this domain was based on the review authors' opinion, which, in turn, was based on ample evidence that amphetamines have intense behavioural and haemodynamic effects that can unmask the intervention being studied (Childs 2009; Johanson 1980; Makris 2004; Makris 2007; Wachtel 1992). Use of a nocebo (i.e. an active placebo that produces noticeable side effects that may convince the person that he/she is being treated with the active drug) has been proposed as a means of reducing the possibility of unblinding (Storebø 2015); however, this type of comparator has ethical problems, as it conflicts with the principle of non-maleficence. A better alternative to nocebos would be the use of objective outcomes (e.g. accidents, legal or work problems), which have a lower risk of performance and detection bias than subjective outcomes (e.g. ADHD symptom severity). Use of objective, clinically meaningful outcomes, such as accidents or legal or work problems, would also improve the external validity of the findings of clinical trials including patients with ADHD. The validity of the outcome variables used to determine the efficacy of amphetamines for ADHD symptoms is an important question. The clinical interpretation of a reduction of 30% in the severity of ADHD symptoms or a change in the number of units on the ADHD Rating Scale is not straightforward. Thus, it would be helpful to use outcomes with greater clinical interpretability to improve our understanding of the effect of an intervention for this disorder; by way of example, one could monitor the proportion of patients achieving 'symptomatic remission' (i.e. the proportion of patients who fail to meet the full ADHD diagnostic criteria) (Biederman 2000; Keck 1998).

Indirectness moreover may have jeopardised the quality of evidence in this review. Indirectness can arise from combining different medications (e.g. different amphetamines), different doses of the same medication, or studies with important follow-up differ-

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ences, thereby hindering the possibility of making precise recommendations. Uncertainties regarding the indirectness of some estimations, the imprecision of some calculations, the existence of statistical heterogeneity, and the possibility of blinding failure mean that no result can be deemed to provide high-quality or moderate-quality evidence. Thus, it is likely that new research may change the main findings of this review.

We ran two post hoc sensitivity analyses excluding studies at unclear or high risk of bias on two specific domains of the Cochrane 'Risk of bias' tool: 'incomplete outcome data' and 'other biases'. These analyses yielded results similar to those of the primary ones, which suggests that our findings are robust against the two potential sources of bias.

Potential biases in the review process

We conducted a comprehensive search across several bibliographic databases and trial registers, without language restrictions. We also contacted the pharmaceutical industry and corresponding authors of included publications to enquire about additional studies that we may have missed. We did not, however, inspect FDA and EMA websites, and thus we cannot rule out the possibility that the review process is biased. However, we found no evidence of reporting bias, as suggested by a symmetrical funnel plot, but it must be highlighted that the sensitivity and precision of these tests are low. We were able to obtain relevant data from almost all studies. We were able to obtain endpoint or change scores or response rates of clinician- or patient-rated scales assessing the severity of ADHD symptoms in ways suitable for meta-analysis, either directly from the study report or from the study authors. In addition, we were able to obtain data on all-cause treatment discontinuation from 17 out of 19 studies.

With regards to the methods used, some studies applied a modified intention-to-treat (ITT) approach, where only participants who provided at least one post-randomisation outcome were included in the efficacy analysis (Adler 2008; Adler 2013; Brams 2012; Spencer 2008; Weisler 2006; Weisler 2017). Not including all randomised participants may cause attrition bias. To minimise this source of bias, we used an ITT approach to calculate the risk ratio (RR) of these studies. Proceeding in this way yields more conservative efficacy results because it assumes that all individuals who left the study did not have the outcome. Provided that most studies provided short-term follow-up, and given that ADHD is a chronic disorder whose severity does not change after short periods of time, it seems reasonable to assume that participants who left the study were not treatment responders. Even if this is not the case, we expect this will have minimal influence on the results because the proportion of participants excluded from the efficacy analysis of those studies that used a modified ITT approach was low (consistently below 3% of the randomised sample).

We advise caution when interpreting the results of between-subgroup comparisons. Given that these comparisons are indirect ones, head-to-head comparisons are needed to confirm their findings.

Agreements and disagreements with other studies or reviews

We rated the quality of the evidence in this review as low to very low (Otasowie 2014; Punja 2016; Storebø 2015), which is comparable with the quality of evidence reported by other Cochrane Reviews on this topic. Factors that limit the validity and quality of the evidence of systematic reviews of pharmacological treatment for ADHD are recurrent and include attrition bias, the possibility of blinding failure, imprecise results, and statistical heterogeneity (Castells 2011b; Castells 2013; Cunill 2016; Otasowie 2014; Peterson 2007; Punja 2016). Improving the quality of studies investigating the efficacy and safety of pharmacological treatment for ADHD has become a priority to increase the reliability of study findings.

AUTHORS' CONCLUSIONS

Implications for practice

Amphetamines appear to improve the severity of attention deficit hyperactivity disorder (ADHD) symptoms in adults in the short term. Nevertheless, compared to placebo, amphetamines do not increase retention in treatment overall and are associated with higher risk of dropping out as the result of adverse events. Furthermore, blinding failure could occur in the included studies, leading to an overestimation of amphetamine efficacy. For this reason, we considered evidence on the efficacy of amphetamines for ADHD in adults, generated by this review, to be of low or very low quality.

Evidence from this review does not provide a sound basis on which to support the use of higher doses of amphetamines or sustained-release formulations to achieve greater efficacy. However, we did find differences between the types of amphetamines used: lisdexamfetamine was efficacious for reducing the severity of ADHD symptoms independently of the rater, but no evidence showed an effect of dexamphetamine or MAS on the severity of ADHD symptoms, respectively, as rated by clinicians or participants. This could provide indirect, low-quality evidence in favour of lisdexamfetamine over dexamphetamine and MAS.

Implications for research

The external validity of studies that have investigated the efficacy of amphetamines for ADHD in adults could be greater. This could be achieved by including patients with comorbid disorders such as substance use disorder or major depressive disorder. Studies with longer follow-up periods are also needed to demonstrate the long-term efficacy of amphetamines.

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Use of objective outcomes that cannot be influenced by blinding failure, such as the number of accidents or problems at work or at home, would improve the reliability of findings. Nevertheless, it must be acknowledged that using these types of outcomes will make studies less feasible because large samples will be needed to demonstrate differences between the interventions studied.

Given that other drugs, such as atomoxetine or methylphenidate, have been shown to reduce ADHD symptoms in adults, it would be of great interest to compare the efficacy of amphetamines versus the efficacy of these interventions.

In addition, changes in comorbidity profiles with current DSM-5 criteria mean that much of the work reviewed will need to be revalidated.

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Current CDPLP members of staff: Geraldine Macdonald (Coordinating Editor); Joanne Duffield (Managing Editor); and Margaret Anderson (Information Specialist).

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adler 2008

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 48 **Country:** USA **Setting:** outpatients **Statistical methods:** modified ITT (participants with ≥ 1 postrandomisation assessment of the ADHD-RS score were included in the efficacy analysis, which consisted of 414 (98.6%) out of 420 randomised participants). Although no statistically significant differences were found in any baseline data, mean differences were calculated after adjustment for baseline score
Participants	**Sample size:** 420 patients with adult ADHD, according to DSM-IV-TR criteria **Psychiatric comorbid disorders:** excluded patients with a comorbid psychiatric diagnosis with significant symptoms that may preclude treatment with lisdexamfetamine **Mean age:** 35.1 years **Gender:** 228 (54.3%) men **Race:** 349 (83.1%) Caucasian **ADHD subtype:** NR
Interventions	4 groups: 1. Lisdexamfetamine (n = 119): 30 mg/d, qd, fixed posology 2. Lisdexamfetamine (n = 117): 50 mg/d, qd, fixed posology (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for weeks 2 to 4) 3. Lisdexamfetamine (n = 122): 70 mg/d, qd, fixed posology (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for week 2 and 70 mg/d for for weeks 3 to 4) 4. Placebo (n = 62) **Psychotherapy:** NR **Duration:** 4 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Clinical impression, assessed with CGI-S and CGI-I scales 3. Proportion of responders, defined as percentage of participants with ≥ 30% reduction in ADHD-RS total score at endpoint or CGI-I score ≤ 2 4. Retention in treatment 5. Proportion of participants withdrawn owing to cardiovascular adverse events
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00334880) **Study start and end dates:** May 2006 to November 2006 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy and safety outcomes. Study authors directed us to Shire, from whom we requested the data again. Shire responded to our email but did not provide us with the additional data **Other comments:** we obtained data on cardiovascular adverse event-related dropouts

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	from a secondary publication (Adler 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Comment:** attrition was low (17%), and last observation carried forward was deemed a suitable method to impute missing data
Selective reporting (reporting bias)	Low risk	**Comment:** outcomes stated in the study protocol are reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

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Adler 2013

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 35 **Country:** USA **Setting:** outpatients **Statistical methods:** modified ITT (participants who took ≥ 1 dose of study medication during the double-blind phase and had ≥ 1 BRIEF-A assessment, which consisted of 154 (95.7%) out of 161 randomised participants)
Participants	**Sample size:** 161 patients with adult ADHD, according to DSM-IV-TR criteria, in a close domicile relationship for the previous 6 months and with a ADHD-RS-IV score ≥ 28 and a BRIEF-A global executive composite T-score ≥ 65 (2 patients (1 in each group) were included with a BRIEF-A score lower than 65) **Psychiatric comorbid disorders:** excluded patients with comorbid psychiatric diagnosis that was uncontrolled or was controlled with prohibited medication **Mean age:** 34.5 years **Gender:** 83 (52.2%) men **Race:** 16 (9.9%) African American; 136 (84.5%) Caucasian; 7 (4.3%) Other **ADHD subtype:** 129 (80.1%) combined; 29 (18%) inattentive; 1 (0.6%) hyperactive-impulsive
Interventions	2 groups: 1. Lisdexamfetamine (n = 80): 4-week dose titration (beginning with 30 mg and titrated in 20-mg/week increments to an optimal dose of up to 70 mg/d) and 6-week maintenance period (up to 70 mg/d). Mean maintenance dose = 56.9 mg/d 2. placebo (n = 81) **Psychotherapy:** not administered **Duration:** 10 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHR-RS-IV 2. Clinical impression, assessed with CGI-I scale 3. Proportion of responders, defined as percentage of participants with CGI-I score ≤ 2 at endpoint 4. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT01101022) **Study start and end dates:** May 2010 to November 2010 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** the sequence was generated using interactive, voice/web response system

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Adler 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	**Comment:** treatment allocation was assigned using interactive voice/web response system
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** attrition was high (45%), and in this scenario, it is unclear whether any method used to impute missing data can provide unbiased results
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol are reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Biederman 2012

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** NR
Participants	**Sample size:** 69 patients with adult ADHD, according to DSM-IV criteria **Psychiatric comorbid disorders:** excluded patients with clinically significant, comorbid psychiatric conditions or using psychotropic medication during the previous month

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Biederman 2012 (*Continued*)

	Mean age: 21.6 years **Gender:** 38 (62%) men **Race:** NR **ADHD subtype:** NR
Interventions	2 groups: 1. Lisdexamfetamine (n = 31): 2-week dose titration (beginning with 30 mg during the first week, followed by 50 mg/d during the second week and up to 70 mg/d during the third week) and 4-week maintenance period (up to 70 mg/d) 2. placebo (n = 30) **Psychotherapy:** not administered **Duration:** 6 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Proportion of responders, defined as percentage of participants with ≥ 30% reduction in ADHD-RS total score and a CGI-I score ≤ 2 at endpoint 3. Depressive symptoms, assessed with HAM-D 4. Anxiety symptoms, assessed with HAM-A 5. Retention in treatment
Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00801229) **Study start and end dates:** December 2008 to July 2010 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Biederman 2012 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was low (12%), and the imputation methods, if any, were not reported
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available. Only the primary outcome was reported. Secondary outcomes reported in the article are those that one would expect from this type of study
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Brams 2012

Methods	**Design:** double-blind, placebo-controlled, randomised withdrawal study **Number of study sites:** 36 **Country:** USA **Setting:** outpatients **Statistical methods:** all randomised participants who received ≥ 1 study dose and had ≥ 1 ADHD-RS-IV and CGI-S assessment
Participants	**Sample size:** 116 patients with adult ADHD, according to DSM-IV criteria, with a baseline ADHD-RS-IV total score < 22 and a CGI-S score ≥ 3, who had received lisdexamfetamine (30, 50, or 70 mg/d) for ≥ 6 months with an acceptable safety profile, and with a body mass index between 18.5 and 40 **Psychiatric comorbid disorders:** excluded patients with comorbid Axis I or II disorders that were uncontrolled with significant symptoms or were controlled with prohibited medications (psychostimulants and amphetamine-like agents, centrally or peripherally acting antihistamines, investigational compounds, clonidine and guanfacine, and herbal preparations), as well as patients at risk of suicide or with a history of suicide attempts **Mean age:** 35.8 years **Gender:** 50 (43.1%) men **Race:** 106 (91.4%) Caucasian; 10 (8.6%) Other **ADHD subtype:** NR

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Brams 2012 (*Continued*)

Interventions	All randomised participants entered an open-label treatment phase with lisdexamfetamine (at participants' stable treatment dose) during 3 weeks. After that, participants were randomised to 2 groups: 1. Lisdexamfetamine (n = 56): at participants' stable treatment dose. Mean dose = 61.2 mg/d 2. Placebo (n = 60) **Psychotherapy:** not administered **Duration:** 6 weeks
Outcomes	1. ADHD symptom severity, assessed with ADHD-RS-IV 2. Proportion of participants with symptom relapse, defined as the percentage of patients with an increase in ADHD-RS ≥ 50% and ≥ 2-point increase in CGI-S at the end of the study 3. Clinical impression, assessed with CGI-S 4. Retention in treatment*
Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00877487) **Study start and end dates:** April 2009 to September 2010 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** *patients that met symptom relapse criteria at any point during the study were actively withdrawn. Therefore, the outcome "retention in treatment" is markedly different from the remaining studies and was not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects

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Brams 2012 (*Continued*)

		(amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** attrition was high (54%), and statistically significant differences in retention across study groups were found
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol are reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Dupaul 2012

Methods	**Design:** double-blind, placebo-controlled, cross-over clinical trial **Number of study sites:** 2 **Country:** USA **Setting:** outpatients **Statistical methods:** per protocol
Participants	**Sample size:** 24 university students with ADHD, according to DSM-IV-TR, who scored at or above the 90th percentile on current symptom ratings based on self-reports **Psychiatric comorbid disorders:** excluded participants with significant symptoms of major depressive disorder, bipolar disorder, or thought disorder with significant illicit substance abuse **Mean age:** 20.2 years **Gender:** 15 (62.5%) men **Race:** 22 (91%) Caucasian **ADHD subtype:** 17 (70.8%) combined; 16 (25%) inattentive; 1 (4.2 %) hyperactive-impulsive
Interventions	4 groups: 1. Lisdexamfetamine (n = 24): 30 mg/d, qd, fixed posology 2. Lisdexamfetamine (n = 24): 50 mg/d, qd, fixed posology 3. Lisdexamfetamine (n = 24): 70 mg/d, qd, fixed posology 4. Placebo (n = 24) **Psychotherapy:** not administered **Duration:** 1 week
Outcomes	1. ADHD symptom severity, assessed with patient-rated CAARS-SF

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Dupaul 2012 (*Continued*)

Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry **Study protocol:** available (NCT01342445) **Study start and end dates:** September 2009 to December 2010 **Declared/potential conflicts of interest:** study authors declared no conflicts of interest, but the study was funded entirely by the pharmaceutical industry **Missing data:** we requested additional data on safety outcomes from the study authors, and they provided us with this information **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Low risk	**Comment:** participants, research assistants, and professors had no access to the randomisation sequence
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** 2 out of 24 participants discontinued treatment and were not included in the statistical analysis
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was available. Adverse events were poorly reported in the clinical trials register and in the article

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Dupaul 2012 (*Continued*)

Other bias	High risk	**Comment:** no washout phase was included. The possibility of a carry-over effect was not studied. Patients were paid to participate

Frick 2017

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 48 **Country:** USA **Setting:** outpatients **Statistical methods:** ITT (all randomised participants taking ≥ 1 study dose and having ≥ 1 postbaseline primary efficacy assessment and a baseline assessment)
Participants	**Sample size:** 411 patients with adult ADHD, according to DSM-IV-TR criteria, with an ADHD-RS-IV score ≥ 32 **Psychiatric comorbid disorders:** excluded patients with Axis I disorders controlled with prohibited medications, or uncontrolled and associated with significant symptoms, or patients with symptoms that could confound clinical assessments at screening **Mean age:** 37.1 years **Gender:** 233 (56.7%) men **Race:** 23 (5.6%) African American; 358 (87.1%) Caucasian; 27 (6.6%) Other **ADHD subtype:** 332 (80.8%) combined; 75 (18.2%) inattentive; 4 (1%) hyperactive-impulsive
Interventions	4 groups: 1. Triple-bead MAS (n = 104): 25 mg/d, qd, fixed posology 2. Triple-bead MAS (n = 101): 50 mg, qd, fixed posology (titration over 2 weeks: 25 mg/d during week 1, 37.5 mg/d during week 2, 50 mg/d during weeks 3 to 6) 3. Triple-bead MAS (n = 102): 75 mg, qd (fixed posology) (titration over 3 weeks: 25 mg/d during week 1, 37.5 mg/d during week 2, 50 mg/d during week 3, 75 mg/d during weeks 4 to 6) 4. Placebo (n = 104) **Psychotherapy:** not administered **Duration:** 6 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Clinical impression, assessed with CGI-I scale 3. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00152022) **Study start and end dates:** April 2005 to April 2006 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

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Frick 2017 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** attrition was moderate (29%) , and statistically significant differences in retention across study groups were found
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	Unclear risk	**Comment:** study groups were balanced at baseline. There was a long period of time (approximately 10 years) between presentation of preliminary results of this study (in 2007 at the 160th annual meeting of the American Psychiatric Association in San Diego) and publication of the article with the main results. In addition, secondary results were published before the primary ones

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Kay 2009

Methods	**Design:** double-blind, placebo-controlled, cross-over, randomised clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** ITT (participants who were randomised to treatment, received ≥ 1 dose of study drug, and completed ≥ 1 test session)
Participants	**Sample size:** 19 patients with ADHD, according to DSM-IV-TR criteria, with an ADHD-RS score ≥ 24, a score ≤ 50th percentile on either the Stroop Color and Word Test or the Halstead-Reitan Category Test, and with valid driver's license and ≥ 3 years of driving experience **Psychiatric comorbid disorders:** excluded patients with a current comorbid psychiatric diagnosis (controlled or uncontrolled) or substance abuse or dependence for the previous 6 months, and patients who were naive to ADHD medications **Mean age:** 22.3 years **Gender:** 17 (89.5%) men **Race:** 2 (10.5%) African American; 15 (78.9%) Caucasian; 2 (10.5%) Other **ADHD subtype:** NR
Interventions	2 groups: 1. MAS XR (n =19): 20 mg/d during the first week, 40 mg/d during the second week, and 50 mg/d during the third week, qd, fixed posology 2. Placebo (n =19) **Psychotherapy:** not administered **Duration:** 3 weeks
Outcomes	1. Proportion of responders, defined as percentage of participants with ≥ 30% reduction in ADHD-RS total score at endpoint 2. Clinical impression, assessed with CGI-I scale 3. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00557960) **Study start and end dates:** February 2004 to October 2004 **Declared/potential conflicts of interest:** NR **Missing data**: we requested additional data on efficacy outcomes but have not obtained them as yet **Other comments:** none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Comment:** a 4-digit randomisation numbers table was used.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.

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Kay 2009 (*Continued*)

Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was moderate (21%), and the imputation methods, if any, were not reported
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	High risk	**Comment:** no washout phase was included. The possibility of a carry-over effect was not studied. Medication-naive patients with ADHD were excluded

Kollins 2014

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** per protocol
Participants	**Sample size:** 32 patients with adult ADHD, according to DSM-IV-TR criteria, and nicotine dependence, smoking at least 10 cigarettes per day and with an expired air CO level $\geq$ 10 ppm **Psychiatric comorbid disorders:** excluded patients with any other psychiatric condition or using illicit drugs (confirmed by urine drug screen) **Mean age:** 31.4 years **Gender:** 20 (62.5%) men

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	Race: 24 (78.1%) Caucasian; 7 (21.9%) Other **ADHD subtype:** 19 (52.4%) combined; 12 (37.5%) inattentive; 1 (3.1%) hyperactive-impulsive
Interventions	2 groups: 1. Lisdexamfetamine (n = 17): 2-week dose titration (beginning with 30 mg and titrated in 20 mg/week increments to an optimal dose of up to 70 mg/d) and 2-week maintenance period (up to 70 mg/d). Mean maintenance dose = 56.9 mg/d 2. Placebo (n = 15) All participants received a transdermal nicotine patch from 2 weeks before randomisation until the end of the study (21 mg nicotine/24 h for the 2 weeks previous to randomisation and the first week after randomisation, 14 mg nicotine/24 h for the second week after randomisation, and 7 mg nicotine/24 h for the last 2 weeks of the study) **Psychotherapy:** not administered **Duration:** 4 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician- and patient-rated CAARS 2. Proportion of responders, defined as percentage of participants with CGI-I score $\leq$ 2 at endpoint 3. Retention in treatment
Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00736255) **Study start and end dates:** December 2007 to July 2011 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy outcomes but have not obtained them as yet **Other comments:** the study was suspended for several months when it was reported by the sponsor that some of the medication that had been provided had reached an expiration date. This affected 2 participants who were discontinued before randomisation and 1 participant who was already started on medication and subsequently was discontinued from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Kollins 2014 (*Continued*)

Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was low (13%), but the analysis was per protocol.
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Levin 2015

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial **Number of study sites:** 2 **Country:** USA **Setting:** outpatients **Statistical method:** ITT
Participants	**Sample size:** 126 patients with adult ADHD, according to DSM-IV-TR criteria, and cocaine dependence **Psychiatric comorbid disorders:** excluded patients with past mania, schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse, patients with an unstable psychiatric condition, or patients currently undergoing treatment **Mean age:** 36.4 years **Gender:** 106 (84.1%) men **Race:** 22 (17.5%) African American; 72 (57.1%) Caucasian; 28 (22.2%) Other **ADHD subtype:** NR
Interventions	3 groups: 1. MAS XR (n = 40): 60 mg/d, qd, fixed posology. Mean tolerated dose = 53.3 mg/d 2. MAS XR (n = 43): 80 mg/d, qd, fixed posology. Mean tolerated dose = 70.8 mg/d 3. Placebo (n = 43)

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Levin 2015 (*Continued*)

	Psychotherapy: all participants also received CBT and relapse prevention. **Duration:** 14 weeks (1-week placebo lead-in phase followed by 13-week trial)
Outcomes	1. ADHD symptom severity, assessed with adult AISRS 2. Clinical impression of severity and improvement, assessed with CGI-S and CGI-I scales, respectively 3. Proportion of responders, defined as percentage of participants with ≥ 30% reduction in AISRS total score at endpoint or CGI-I score ≤ 2 4. Retention in treatment
Notes	**Author's affiliation:** university **Study funding:** public **Study protocol:** available (NCT00553319) **Study start and end dates:** December 2007 to July 2013 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** the random sequence was computer-generated.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Levin 2015 (*Continued*)

Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was moderate (26%) , and last observation carried forward was deemed a suitable method to impute missing data
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Martin 2014a

Methods	**Design:** double-blind, placebo-controlled, 3-period, cross-over, randomised clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** seem to be per protocol. Study completers (17 out of 18) were included in the efficacy analysis
Participants	**Sample size:** 18 adults aged 18 to 55 years with ADHD, according to DSM-IV criteria, and with a history of successful treatment with an amphetamine-based agent **Psychiatric comorbid disorders:** excluded patients with a diagnosis of severe, comorbid Axis I or Axis II disorder **Mean age:** 30.8 years **Gender:** 11 (61.1%) men **Race:** 15 (83.3%) Caucasian **ADHD subtype:** NR
Interventions	3 groups: 1. Lisdexamfetamine (n = 18): 50 mg/d, fixed posology 2. MAS-IR (n = 18): 20 mg/d, fixed posology 3. Placebo (n = 18) **Psychotherapy:** not administered **Duration:** 1 week with each study intervention. No washout period was scheduled
Outcomes	1. ADHD symptom severity, assessed with the patient-rated CAARS: Short Version 2. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT01010750) **Study start and end dates:** January 2010 to April 2010 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

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Martin 2014a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** study had a cross-over design, and it seems that a paired data analysis was conducted under a per-protocol principle. Nevertheless, attrition was low (1 participant)
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	High risk	**Comment:** no washout phase was included. The possibility of a carry-over effect was not studied. All participants had a history of responsiveness to amphetamines

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Martin 2014b

Methods	**Design:** double-blind, placebo-controlled, 3-period, cross-over, randomised clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** seem to be per protocol. Study completers (17 out of 18) were included in the efficacy analysis
Participants	**Sample size:** 18 adults aged 18 to 55 years with ADHD, according to DSM-IV criteria, and with a history of successful treatment with an amphetamine-based agent **Psychiatric comorbid disorders:** excluded patients with a diagnosis of severe, comorbid Axis I or II disorder **Mean age:** 30.8 years **Gender:** 11 (61.1%) men **Race:** 15 (83.3%) Caucasian **ADHD subtype:** NR
Interventions	3 groups: 1. Lisdexamfetamine (n = 18): 50 mg/d, fixed posology 2. MAS-IR (n = 18): 20 mg/d, fixed posology 3. Placebo (n = 18) **Psychotherapy:** not administered **Duration:** 1 week with each study intervention. No washout period was scheduled
Outcomes	1. ADHD symptom severity, assessed with the patient-rated CAARS: Short Version 2. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT01010750) **Study start and end dates:** January 2010 to April 2010 **Declared/potential conflicts of interest:** yes **Missing data:** we did not request additional data from the study authors. **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Martin 2014b (*Continued*)

Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** study had a cross-over design, and it seems that a paired data analysis was conducted under a per-protocol principle. Nevertheless, attrition was low (1 participant)
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	High risk	**Comment:** no washout phase was included. The possibility of a carry-over effect was not studied. All participants had a history of responsiveness to amphetamines

Spencer 2001

Methods	**Design:** double-blind, placebo-controlled, randomised, cross-over trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** per-protocol analysis
Participants	**Sample size:** 30 patients with adult ADHD, according to DSM-IV criteria. The per-protocol sample consisted of 27 (90%) patients **Psychiatric comorbid disorders:** excluded patients with an IQ < 80, delirium, dementia, amnesic disorders, any other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis), drug or alcohol abuse or dependence within the 6 months preceding the study, or currently using psychotropics **Mean age:** 38 years **Gender:** 15 (55.6%) men **Race:** 26 (96%) Caucasian

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Spencer 2001 (*Continued*)

	ADHD subtype: 12 (44%) combined; 15 (56%) inattentive; 0 hyperactive-impulsive
Interventions	2 groups: 1. MAS-IR (n = 30): 3-week, stepwise dose titration (20 mg/d (10 mg twice daily) by week 1, 40 mg/d (20 mg twice daily) by week 2, 60 mg/d (30 mg twice daily) by week 3, unless adverse effects emerged). Mean dose across the study = 37.4 mg/d, mean dose at study completion = 53.7 mg/d 2. Placebo (n = 30) **Psychotherapy:** not administered **Duration:** 3 weeks (2 × 3-week-long periods separated by 1 week of washout)
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Clinical impression of severity and improvement, assessed with CGI-S and CGI-I, respectively 3. Proportion of responders, defined as percentage of participants with ≥ 30% reduction in ADHD-RS total score at endpoint or CGI-I score ≤ 2 4. Depressive symptom severity, assessed with HAM-D and BDI 5. Anxiety symptom severity, assessed with HAM-A 6. Retention in treatment
Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry and public funds **Study protocol:** not available **Study start and end dates:** NR **Declared/potential conflicts of interest:** NR **Missing data**: we requested additional data on efficacy outcomes from the study authors. Study authors directed us to Shire, from whom we requested the data again. Shire responded to our email but did not provide us with the additional data **Other comments:** a carry-over effect was observed, which can lead to biased results. To avoid the influence of this bias, it is recommended to use data from the first period of the study, as if it was a parallel-group clinical trial. However, data from the first period were available only for retention in treatment. We requested the remaining outcome data but were not able to obtain them. The carry-over effect can underestimate the effect of the intervention and can bias the result towards the null for both effectiveness and adverse events outcomes. To determine whether this study could bias the results of our meta-analysis, we conducted a sensitivity analysis in which we repeated the analysis with this study excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.

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Spencer 2001 (*Continued*)

Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** study had a cross-over design, and it seems that a paired data analysis was conducted under a per-protocol principle. Nevertheless, attrition was low (10%)
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and the possibility of reporting bias could not be assessed
Other bias	High risk	**Comment:** a carry-over effect was observed, and data from the first study period were not available

Spencer 2008

Methods	**Design:** double-blind, randomised, placebo-controlled, parallel-group clinical trial **Number of study sites:** 39 **Country:** USA **Setting:** outpatients **Statistical analysis:** modified ITT; 268 (97.8%) participants (out of 274 who were randomised) were included in the efficacy analysis. 6 participants were excluded from the efficacy analysis because they discontinued the study before the first assessment. Although no statistically significant differences were found in any baseline data, mean differences were calculated after adjustment for baseline score. Unadjusted mean differences were also reported, which did not differ from the adjusted ones

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Spencer 2008 (*Continued*)

Participants	**Sample size:** 274 patients with adult ADHD, according to DSM-IV-TR criteria, with a baseline ADHD-RS score ≥ 24 **Psychiatric comorbid disorders:** excluded patients with any psychiatric disorder with, in the opinion of the investigator, significant symptoms and substance use disorder (except nicotine dependence) within the 6 months preceding the screening **Mean age:** 36.5 years **Gender:** 136 (50%) men **Race:** 21 (7.7%) African American; 231 (84.9%) Caucasian; 20 (7.4%) Other **ADHD subtype:** 192 (70.6%) combined; 72 (26.5%) inattentive; 8 (2.9%) hyperactive-impulsive
Interventions	2 parallel groups: 1. Triple-bead MAS (n = 137): 5-week, stepwise dose titration (beginning with 12.5 mg/d and maximum dose 75 mg/d) followed by 2-week maintenance dose, administered qd). Mean maintenance dose = 47.9 mg/d 2. Placebo (n = 137) **Psychotherapy:** not administered **Duration:** 7 weeks
Outcomes	1. ADHD symptom severity, assessed by clinician-rated ADHD-RS 2. Clinical impression of severity and improvement, assessed with CGI-S and CGI-I, respectively 3. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** NCT00150579 **Study start and end dates:** January 2005 to December 2005 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on safety outcomes from the study authors. Study authors directed us to Shire, from whom we requested the data again. Shire responded to our email but did not provide us with the additional data **Other comments:** unpublished data sought but not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Spencer 2008 (*Continued*)

Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** attrition was moderate (38%) , and statistically significant differences in retention across study groups were found
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol are reported in the article
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Taylor 2000

Methods	**Design:** double-blind, randomised, placebo-controlled, cross-over clinical trial **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical analysis:** ITT (all randomised participants were included in the statistical analysis)
Participants	**Sample size:** 22 patients with adult ADHD, according to DSM-IV criteria. To be eligible, patients had to score above the 93th percentile on both adult and childhood versions of the DSM-IV-based ADHD Behaviour Checklist **Psychiatric comorbid disorders:** excluded patients with schizophrenia and Tourette disorder, as well as cannabis, cocaine, non-prescription amphetamine, or heroin users during the past 6 months **Mean age:** 40.8 years **Gender:** 13 (59%) men **Race:** NR **ADHD subtype:** 9 (41%) combined; 11 (50%) inattentive; 2 (9%) hyperactive-impulsive

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Taylor 2000 (*Continued*)

Interventions	3 groups: 1. Dextroamphetamine (n = 22): 5 to 20 mg bid. Dose was titrated up using 5-mg increments every 1 or 2 days, as tolerated, to a maximum of 20 mg bid. Titration was achieved within 4 to 7 days and was maintained for an additional 4 to 10 days. Average dose was 21.8 mg/d. 2. Modafinil (n = 22): 50 to 200 mg bid. Dose was titrated up using 50-mg increments every 1 or 2 days, as tolerated, to a maximum of 200 mg bid. Titration was achieved within 4 to 7 days and was maintained for an additional 4 to 10 days. 3. Placebo (n = 22) **Psychotherapy:** not administered **Duration:** 50 days (3 × 14-day treatment periods separated by 2 × 4-day washout periods)
Outcomes	1. ADHD symptom severity, assessed with "self-rated DSM-IV ADHD behaviour checklist for adults" 2. Depressive symptom severity, assessed with 21-item BDI 3. Anxiety symptom severity, assessed with 14-item HAM-A 4. Retention in treatment
Notes	**Author affiliation:** university and health care system **Study funding:** NR **Study protocol:** not available **Study start and end dates:** NR **Declared/potential conflicts of interest:** NR **Missing data:** we requested additional data on efficacy outcomes from the study authors, and they provided us with this information **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Taylor 2000 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Comment:** attrition was low (5%), and last observation carried forward was used to impute missing data
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and the possibility of reporting bias could not be assessed
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Taylor 2001

Methods	**Design:** double-blind, randomised, placebo-controlled, cross-over clinical trial **Number of sites:** 1 **Country:** USA **Setting:** outpatients **Statistical analysis:** ITT (all randomised participants were included in the statistical analysis)
Participants	**Sample size:** 17 patients with adult ADHD, according to DSM-IV criteria. To be eligible, patients had to score above the 93th percentile on both adult and childhood versions of the DSM-IV-based ADHD Behaviour Checklist **Psychiatric comorbid disorders:** excluded patients with organic brain disorders, schizophrenia, and Tourette disorder, as well as cannabis, cocaine, amphetamine, or heroin users during the past 6 months **Mean age:** 41.2 years **Gender:** 7 (41%%) men **Race:** NR **ADHD subtype:** NR
Interventions	3 groups: 1. Dextroamphetamine (n = 17): 2.5 to 20 mg qd. Dose was titrated up using 2.5-mg increments every 2 days, as tolerated, to a maximum of 20 mg/d. Titration was achieved within 4 to 7 days and was maintained for an additional 4 to 10 days. Average dose was 10.2 mg/d. A short-acting pharmaceutical presentation was used. 2. Guanfacine (n = 17): 0.25 to 2.0 mg qd. Dose was titrated up using 0.25-mg

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	increments every 2 days, as tolerated, to a maximum of 2.0 mg/d. Titration was achieved within 4 to 7 days and was maintained for an additional 4 to 10 days. 3. Placebo (n = 17) **Psychotherapy:** not administered **Duration:** 50 days (3 × 14-day treatment periods separated by 2 × 4-day washout periods)
Outcomes	1. ADHD symptom severity, assessed with "self-rated DSM-IV ADHD behaviour checklist for adults" 2. Depressive symptom severity, assessed with 21-item BDI 3. Anxiety symptom severity, assessed with 14-item HAM-A 4. Retention in treatment
Notes	**Author affiliation:** university and health care system **Study funding:** NR **Study protocol:** not available **Study start and end dates:** NR **Declared/potential conflicts of interest:** NR **Missing data:** we requested additional data on efficacy outcomes from the study authors, and they provided us with this information **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects

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Taylor 2001 (*Continued*)

		(amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Comment:** no participant dropped out.
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and the possibility of reporting bias could not be assessed
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Waxmonsky 2014

Methods	**Design:** double-blind, placebo-controlled, randomised clinical trial with an open-label dose-optimisation phase **Number of study sites:** 1 **Country:** USA **Setting:** outpatients **Statistical methods:** unclear
Participants	**Sample size:** 27 adults with ADHD, according to DSM-IV criteria, with an ADHD-RS score $\geq$ 28 and a CGI-S score $\geq$ 4, who had a child between 5 and 12 years old with a diagnosis of ADHD, according to DSM-IV criteria, and with a minimum score of 5 on the Sheehan Disability Scale **Psychiatric comorbid disorders:** excluded patients with comorbid psychiatric conditions that could worsen with stimulants and those who required psychotropic medications **Mean age:** 41.04 years **Gender:** 7 (25.9 %) men **Race:** NR **ADHD subtype:** NR
Interventions	All participants entered a 3-week, open-label, dose-optimisation phase, during which they received lisdexamfetamine that was initiated at 30 mg/d and could be increased to 50 mg/d during the second week, and to 70 mg/d during the third week, depending on efficacy and tolerability. Optimal dose was defined as a physically tolerable dose that produced a $\geq$ 30% reduction in the ADHD-RS-IV score and a CGI-I rating of 1 or 2. After that, participants entered a 2-week, within-subject evaluation of 2 parent-child interaction tasks - 1 while taking lisdexamfetamine and 1 while taking placebo. Between tasks, participants were allowed to receive their optimal lisdexamfetamine dose. After this phase, participants were randomised to: 1. Lisdexamfetamine (n = 13): at participant's optimal dose. Mean maintenance dose = 54.5 mg/d 2. Placebo (n = 14) **Psychotherapy:** not administered **Duration:** 4 weeks

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Outcomes	1. ADHD symptoms, assessed by clinician-rated ADHD-RS-IV 2. Proportion of responders, defined as percentage of participants with CGI-I score ≤ 2 at endpoint 3. Retention to treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT01127607) **Study start and end dates:** November 2010 to July 2012 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy outcomes but have not yet obtained this information **Other comments:** data on ADHD symptom severity were obtained from clinical trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was low (11%), and the imputation methods, if any, were not reported

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Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	High risk	**Comment:** before the double-blind phase came a run-in phase with lisdexamfetamine (up to 70 mg/d), in which 8 participants discontinued - 5 because of adverse events. Thus, it seems that there might have been a pre-selection of tolerant patients, which could have biased safety results. In addition, we found inconsistent data on discontinuation between results reported in clinical trials and those described in the article. This inconsistency could not be clarified by contacting the study authors

Weisler 2006

Methods	**Design:** multi-site, double-blind, randomised, placebo-controlled, parallel-group clinical trial **Number of study sites:** 18 **Country:** USA **Setting:** outpatients **Statistical analysis:** modified ITT; 248 (97.3%) participants (out of 255 who were randomised) were included in the efficacy analysis. The reasons for excluding 7 participants from the ITT analysis were not reported
Participants	**Sample size:** 255 patients with adult ADHD (combined type), according to DSM-IV-TR criteria **Psychiatric comorbid disorders:** excluded patients with an IQ < 80 and those with comorbid psychosis, bipolar illness, pervasive developmental disorder, or severe obsessive-compulsive disorder, as well as severe depressive (17-item HAM-D score > 19) and anxiety disorders (14-item HAM-A score > 17). Also excluded participants who tested positive on drug screening, with a history of substance abuse, or living with someone with a substance abuse disorder **Mean age:** 39.2 years **Gender:** 149 (60.1%) men **Race:** 8 (3.2%) African American; 221 (89.1%) Caucasian; 19 (7.7%) Other **ADHD subtype:** 255 (100%) combined
Interventions	4 parallel groups: 1. MAS XR (n = 66): 20 mg/d, qd, fixed posology 2. MAS XR (n = 64): 40 mg/d, qd, fixed posology 3. MAS XR (n = 61): 60 mg/d, qd, fixed posology 4. Placebo (n = 64) **Psychotherapy:** not administered **Duration:** 4 weeks

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Outcomes	1. ADHD severity, assessed with clinician- and patient-rated ADHD-RS-IV 2. Clinical impression of severity and improvement, assessed with CGI-S and CGI-I scales, respectively 3. Retention in treatment
Notes	**Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** not available **Study start and end dates:** February 2002 to May 2002 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy outcomes from the study authors. Study authors directed us to Shire, from whom we requested the data again. Shire responded to our email but did not provide us with the additional data **Other comments:** mean (SD) ADHD symptom severity at study completion was reported for the active treatment group but not for the placebo group. Nevertheless, the effect size was available, and we used these data to calculate ADHD symptom severity at study completion for the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo

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Weisler 2006 (*Continued*)

Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was moderate (28%) , and last observation carried forward was used to address missing data
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and the possibility of reporting bias could not be assessed
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Weisler 2017

Methods	**Design:** double-blind, multi-centre, placebo-controlled, randomised clinical trial **Number of study sites:** 43 **Country:** USA **Setting:** outpatients **Statistical methods:** all screened participants assigned a randomisation number, who took 1 or more study drug doses, and who had 1 or more postbaseline, on-treatment, primary efficacy assessments were included in the efficacy analysis
Participants	**Sample size:** 275 patients with adult ADHD, according to DSM-V criteria, with a baseline ADHD-RS-AP total score ≥ 28 **Psychiatric comorbid disorders:** excluded patients with a comorbid psychiatric diagnosis that was controlled with prohibited medications (psychostimulants and amphetamine-like agents, centrally or peripherally acting antihistamines, investigational compounds, clonidine and guanfacine, and herbal preparations), or was uncontrolled and was associated with significant symptoms that contraindicated MAS treatment or could confound study assessments. Also excluded patients with suicide risk and those who had previously attempted suicide **Mean age:** 33.6 years **Gender:** 156 (57.6%) men **Race:** 23 (8.5%) African American; 221 (57.6%) Caucasian; 27 (10%) Other **ADHD subtype:** 219 (80.8%) combined; 50 (18.5%) inattentive; 2 (0.73%) hyperactive-impulsive
Interventions	3 groups: 1. Triple-bead MAS (n = 92): 12.5 mg/d, qd, fixed posology 2. Triple-bead MAS (n = 92): 37.5 mg/d, qd, fixed posology (titration over 2 weeks: 12.5 mg/d during week 1, 25 mg/d during week 2, 37.5 mg/d from weeks 3 and 4) 3. Placebo (n = 91) **Psychotherapy:** not administered **Duration:** 4 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-AP 2. Clinical impression of improvement, assessed with CGI-I scale

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Notes	**Authors; affiliations:** university and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT02604407) **Study start and end dates:** November 2015 to March 2016 **Declared/potential conflicts of interest:** yes **Missing data:** none **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** treatment assignments were made by an interactive, web response system
Allocation concealment (selection bias)	Low risk	**Comment:** investigators, investigators' staff, and participants were blinded to the treatment assignment
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was low (14%), and imputation methods, if any, were not reported
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol are reported in the article

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Weisler 2017 (*Continued*)

Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

Weiss 2006

Methods	**Design:** double-blind, randomised, placebo-controlled, parallel-group, clinical trial **Number of study sites:** 5 **Country:** USA and Canada **Seting:** outpatients **Statistical analysis:** ITT (all randomised participants were included in the statistical analysis)
Participants	**Sample size:** 98 patients with adult ADHD, according to DSM-IV criteria **Psychiatric comorbid disorders:** excluded patients with comorbid psychosis, eating disorders, substance abuse disorders, organic brain syndrome, and active suicide risk. Permitted other comorbid disorders if they did not require treatment with psychotropic medications other than those provided for in the protocol **Mean age:** 37.5 years **Gender:** 63 (64%) men **Race:** 83 (85%) Caucasian; 15 (15%) Other **ADHD subtype:** 59 (60%) combined; 35 (36%) inattentive; 4 (4%) hyperactive-impulsive
Interventions	4 parallel groups: 1. Dexamphetamine (n = 23): 4-week dose titration (beginning with 5 mg bid and maximum dose 20 mg bid) followed by 16-week maintenance dose 2. Paroxetine (n = 24): 4-week dose titration (beginning with 20 mg qd and maximum dose 40 mg qd) followed by 16-week maintenance dose 3. Paroxetine + dexamphetamine (n = 25*) 4. Placebo (n = 26) **Psychotherapy:** 9 sessions of problem-focused psychotherapy **Duration:** 20 weeks
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Clinical impression, assessed with CGI-I 3. Anxiety symptom severity, assessed with HAM-A 4. Depressive symptom severity, assessed with HAM-D 5. Global activity functioning
Notes	**Author's affiliation:** university **Study funding:** pharmaceutical industry **Study protocol:** not available **Study start and end dates:** NR **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy outcomes from the study authors, and they provided us with this information **Other comments:** *outcome data from this group were not included in this systematic

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	review	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was moderate (35%), and in this scenario, it is unclear whether any method used to impute missing data can provide unbiased results
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and the possibility of reporting bias could not be assessed
Other bias	Low risk	**Comment:** study groups were balanced at baseline. The study appears free of other biases

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Wigal 2010

Methods	**Design:** double-blind, placebo-controlled, cross-over, randomised clinical trial with an open-label dose-optimisation phase **Number of study sites:** 5 **Country:** USA **Setting:** outpatients **Statistical methods:** per protocol
Participants	**Sample size:** 142 adults with a diagnosis of ADHD, according to DSM-IV-TR criteria **Psychiatric comorbid disorders:** excluded participants with a comorbid psychiatric diagnosis with significant symptoms, with comorbid substance abuse, or at risk of suicide, or who showed a lack of response to previous amphetamine therapy **Mean age:** 30.5 years **Gender:** 88 (62%) men **Race:** 6 (4.2%) African American; 127 (89.4%) Caucasian; 9 (6.3%) Other **ADHD subtype:** 98 (69%) combined; 39 (27.5%) inattentive; 5 (3.5%) hyperactive-impulsive
Interventions	All participants entered a 4-week, open-label dose-optimisation phase, during which they received lisdexamfetamine, which was initiated at 30 mg/d and was upwardly titrated to 70 mg/d depending on efficacy and tolerability. Only participants who tolerated lisdexamfetamine and showed marked improvement in ADHD symptoms (response with ≥ 30% reduction in ADHD-RS-IV score and a CGI-I rating of 1 or 2, very much or much improved) were randomised to 2 groups: 1. Lisdexamfetamine (n = 63): at the optimised dose during the open-label phase. Mean maintenance dose: 52.3 mg/d 2. Placebo (n = 64) **Psychotherapy:** not administered **Duration:** 1 week
Outcomes	1. ADHD symptom severity, assessed with clinician-rated ADHD-RS-IV 2. Clinical impression, assessed with CGI-I scale 3. Retention to treatment
Notes	**Author's affiliation:** university, healthcare and pharmaceutical industry **Study funding:** pharmaceutical industry **Study protocol:** available (NCT00697515) **Study start and end dates:** July 2008 to December 2008 **Declared/potential conflicts of interest:** yes **Missing data:** we requested additional data on efficacy outcomes but have not yet obtained this information **Other comments:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** the sequence generation method is not described.

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Wigal 2010 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Comment:** the method of allocation concealment is not described.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of participants and personnel (performance bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Blinding of outcome assessment (detection bias) Retention to treatment	Unclear risk	**Comment:** it is unclear whether blinding can be achieved when study medications with powerful behavioural effects (amphetamines) are compared to placebo
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** attrition was low (19%), and the statistical analysis was per protocol
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol was available, and outcomes stated in the protocol were reported in the article
Other bias	High risk	**Comment:** no washout phase was included. The possibility of a carry-over effect was not studied. Patients with a history of non-response to amphetamines were excluded. All participants took lisdexamfetamine (up to 70 mg/d) during a run-in phase before they were randomised to the study interventions

ADHD: attention deficit hyperactivity disorder; **ADHD:RS-AP:** Attention Deficit Hyperactivity Disorder Rating Scale With Adult Prompts; **ADHD-RS:** Attention Deficit Hyperactivity Disorder Rating Scale; **ADHD-RS-IV:** Attention Deficit Hyperactivity Disorder Rating Scale, Fourth Version; **AE:** adverse events; **AISRS:** Adult Attention Deficity Hyperactivity Disorder Investigator Rating Scale; **BDI:** Beck Depression Inventory; **BRIEF:** Behavior Rating Inventory of Executive Function; **BRIEF-A:** Behavior Rating Inventory of Executive Function - Adult Version; **CAARS:** Conners' Adult ADHD Rating Scale; **CAARS-SF:** Conners' Adult ADHD Rating Scale - Short Form; **CBT:** cognitive-behavioural therapy; **CGI-I:** Clinical Global Impressions - Improvement scale; **CGI-S:** Clinical Global Impressions - Severity scale; **CO:** carbon monoxide; **DSM:** *Diagnostic and Statistical Manual of Mental Disorders;* **DSM-IV:** *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition;* **DSM-IV-TR:** *Diagnostic and*

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Statistical Manual of Mental Disorders - Fourth Edition - Text Revision; **DSM-5:** *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;* **HAM-A:** Hamilton Anxiety Rating scale; **HAM-D:** Hamilton Depression Rating scale;**IQ:** intelligence quotient; **ITT:** intention-to-treat; **MAS:** mixed amphetamine salts; **MAS-IR:** mixed amphetamine salts - immediate release; **MAS-ER:** mixed amphetamine salts - extended release; **NR:** not reported; **QD:** once a day; **SD:** standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adler 2011	Not controlled with placebo or active control. RCT comparing MAS-IR and MAS-XR
Adler 2014	Not an RCT
Arnold 1972	Not an RCT
Castaneda 2000	Not an RCT
Dodson 2005	Not an RCT
Faraone 2002	Study participants were children with ADHD.
Goodman 2005	Not an RCT
Lasser 2010	Not an RCT
Mattingly 2012	Not an RCT
Paterson 1999	Used subthreshold, DSM-IV criteria for ADHD
Rostain 2009	Not an RCT
Spencer 2004	Not an RCT
Waxmonsky 2011	Not an RCT
Weisler 2014	Not an RCT
Wiebe 2010	Study participants were children with ADHD.
Wilens 2005	Not an RCT
Young 2015	RCT assessing cognitive-behavioural therapy, not amphetamines

ADHD: attention deficit hyperactivity disorder; **DSM-IV:** *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* **MAS-IR:** mixed amphetamine salts - immediate release; **MAS-ER:** mixed amphetamine salts - extended release**; RCT:** randomised controlled trial.

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Characteristics of ongoing studies *[ordered by study ID]*

NCT00202605

Trial name or title	A phase II, randomised, double-blind, multi-centre, placebo-controlled, cross-over study of SPD465 in adults with attention deficit hyperactivity disorder (ADHD)
Methods	Phase II, randomised, double-blind, multi-centre, placebo-controlled, cross-over study
Participants	Adults with ADHD, using DSM-IV-TR criteria, with a baseline ADHD-RS-IV score ≥ 24
Interventions	1. SPD465 (triple-bead MAS) 2. Placebo
Outcomes	1. Time Segment Rating System 2. Participant self-report of ADHD 3. Treatment-emergent adverse events 4. Sleep quality
Starting date	**Status:** completed **Study start date:** September 2005 **Study end date:** April 2006 **Last updated:** November 2007
Contact information	**Principal investigator:** not specified **Contact name(s):** not provided **Telephone number(s):** not provided **Address:** not provided **Email(s):** not provided **Sponsor/collaborator:** Shire Pharmaceuticals
Notes	NCT00202605

NCT00514202

Trial name or title	Pilot study examining effect for dextroamphetamine to treat cocaine dependence plus attention deficit hyperactivity disorder (ADHD)
Methods	Random allocation, double-blind, 12 weeks' duration, 2 parallel groups, placebo-controlled, phase II
Participants	Patients with ADHD who are cocaine dependent
Interventions	1. Dextroamphetamine SR 60 mg/d 2. Placebo + CBT
Outcomes	1. Substance use 2. ADHD symptoms 3. Treatment retention 4. Cocaine craving

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NCT00514202 (*Continued*)

Starting date	**Status:** completed **Study start date:** August 2007 **Study end date:** October 2008 **Last updated:** February 2012
Contact information	**Principal investigator:** David V Herin **Contact name(s):** not provided **Telephone number(s):** not provided **Address:** The University of Texas Health Science Center, Houston, Texas, USA **Email(s):** not provided **Sponsor/collaborator:** The University of Texas Health Science Center, Houston, Texas, USA
Notes	NCT00514202

NCT00928148

Trial name or title	A phase II, randomised, double-blind, multi-centre, placebo- and active-controlled, cross-over study of SPD465 in adults with attention deficit hyperactivity disorder
Methods	Random allocation, double-blind, 1 week's duration, cross-over assignment, placebo-controlled, phase II
Participants	Adults with ADHD
Interventions	1. SPD465 (triple-bead MAS) 2. Immediate-release amphetamine salt 3. Placebo
Outcomes	1. ADHD symptoms 2. Quality of sleep 3. Performance
Starting date	**Status:** completed **Study start date:** March 2004 **Study end date:** October 2004 **Last updated:** June 2009
Contact information	**Principal investigator:** not provided but the responsible party is Timothy Whitaker, MD, Shire Pharmaceuticals **Contact name(s):** not provided **Telephone number(s):** not provided **Address:** not provided **Email(s):** not provided **Sponsor/collaborator:** not provided
Notes	NCT00928148

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NCT01863459

Trial name or title	Lisdexamfetamine dimesylate in the treatment of adult ADHD with anxiety disorder comorbidity
Methods	Random allocation, double-blind, 18 weeks' duration, cross-over assignment, placebo-controlled, phase IV
Participants	Adults with ADHD and anxiety disorder
Interventions	1. Lisdexamfetamine 2. Placebo
Outcomes	1. ADHD symptoms 2. Anxiety symptoms 3. Depressive symptoms 4. Quality of life 5. Quality of sleep 6. Disability
Starting date	**Status:** completed **Study start date:** April 2013 **Study end date:** March 2017 **Last updated:** August 2017
Contact information	**Principal investigator:** Stephen Collins **Contact name(s):** not provided **Telephone number(s):** not provided **Address:** Centre for Anxiety, Attention Deficit and Trauma, Hamilton, Ontario, Canada **Email(s):** not provided **Sponsor/collaborator:** Centre for Anxiety, Attention Deficit and Trauma, Ontario, Canada; Shire
Notes	NCT01863459

NCT02635035

Trial name or title	Efficacy of lisdexamfetamine in adults with attention deficit hyperactivity disorder (ADHD) and sluggish cognitive tempo
Methods	Random allocation, double-blind, 10 weeks' duration, cross-over assignment, placebo-controlled, phase II
Participants	Adults with ADHD and sluggish cognitive tempo
Interventions	1. Lisdexamfetamine 2. Placebo
Outcomes	1. ADHD symptoms 2. Reaction time 3. Arousal 4. Motivation

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NCT02635035 (*Continued*)

Starting date	**Status:** recruiting **Study start date:** November 2015 **Estimated study end date:** June 2019 **Last updated:** January 2017
Contact information	**Principal investigator:** Lenard Adler **Contact name(s):** Glenn Hirsch, MD; Terry Leon, MD **Telephone number(s):** +1 646 754 4837 **Address:** New York University School of Medicine, New York, USA **Email(s):** hirscg01@nyumc.org; guzmat01@nyumc.org **Sponsor/collaborator:** New York University School of Medicine; Shire
Notes	NCT02635035

NCT02803229

Trial name or title	Treatment of cannabis use disorder among adults with comorbid attention-deficit/hyperactivity disorder
Methods	Random allocation, double-blind, 12 weeks' duration, 2 parallel groups, placebo-controlled, phases II and III
Participants	Adults with ADHD and cannabis use disorder
Interventions	1. Adderall-XR 2. Placebo
Outcomes	1. Cannabis use 2. ADHD symptoms 3. Treatment retention
Starting date	**Status:** recruiting **Study start date:** July 2016 **Estimated study end date:** September 2018 **Last updated:** April 2017
Contact information	**Principal investigator:** Frances R Levin, MD **Contact name(s):** Amy Mahony, LMHC; Elizabeth Martinez **Telephone number(s):** 646-774-8183; 212-923-3031 **Address:** New York Psychiatric Institute, New York, USA **Email(s):** Amy.mahony@nyspi.columbia.edu **Sponsor/collaborator:** New York State Psychiatric Institute; National Institute on Drug Abuse (NIDA)
Notes	NCT02803229

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NCT03153488

Trial name or title	Attention deficit hyperactivity disorder (ADHD) prediction of treatment response
Methods	Random allocation, not blinded, 24 weeks' duration, parallel assignment, active control, phase IV
Participants	Adults with ADHD
Interventions	1. MAS XR 2. Methylphenidate LA
Outcomes	1. CGI-I scale 2. CGI-S scale 3. MRI
Starting date	**Status:** not yet recruiting **Anticipated study start date:** December 2017 **Estimated study end date:** December 2019 **Last updated:** August 2017
Contact information	**Principal investigator:** Joseph Biederman, MD **Contact name(s):** Elizabeth Noyes; Alexa P Pulli, BS **Telephone number(s):** 617-724-2551; 617-726-4651 **Address:** Massachusetts General Hospital, Boston, Massachusetts, USA **Email(s):** enoyes@partners.org; apulli@partners.org **Sponsor/collaborator:** Massachusetts General Hospital; Massachusetts Institute of Technology
Notes	NCT03153488

ADHD: attention deficit hyperactivity disorder; **ADHD-RS-IV:** Attention Deficit Hyperactivity Disorder - Rating Scale - Fourth Version; **CBT:** cognitive-behavioural therapy; **CGI-I:** Clinical Global Impression - Improvement;**CGI-S:** Clinical Global Impression - Severity; **DSM-IV-TR:** *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition - Text Revision*; **LA:** long-acting; **MAS:** mixed amphetamine salts; **MAS-XR:** mixed amphetamine salts - extended release; **MRI:** magnetic resonance imaging; **XR:** extended release.

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DATA AND ANALYSES

Comparison 1. Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician-rated	13		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.04, -0.75]
2 ADHD symptom severity: patient-rated	6		Std. Mean Difference (Random, 95% CI)	-0.51 [-0.75, -0.28]
3 Clinical impression of severity at study end	2	78	Std. Mean Difference (IV, Random, 95% CI)	-1.09 [-1.57, -0.61]
4 Clinical impression of improvement at study end	1	263	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.01, -0.48]
5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms	2	381	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.19, 1.95]
6 Proportion of participants achieving a CGI-Improvement score of 1 or 2	8	1707	Risk Ratio (M-H, Random, 95% CI)	2.47 [2.10, 2.90]
7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2	1	61	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.34, 4.82]
8 Global functioning	2	110	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.34, 1.42]
9 Depressive symptoms	2	110	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.22, 0.53]
10 Anxiety symptoms	2	110	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.24, 0.51]
11 Retention in treatment	17	2323	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
11.1 Dexamphetamine	1	49	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.17]
11.2 Lisdexamfetamine	8	873	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
11.3 Mixed amphetamine salts	8	1401	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
12 Proportion of participants withdrawn owing to any cardiovascular adverse event	3	699	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.39, 12.04]
13 Proportion of participants withdrawn owing to any adverse event	17	2409	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.64, 4.42]
13.1 Dexamphetamine	1	49	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.31, 9.27]
13.2 Lisdexamfetamine	9	989	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.72, 4.42]
13.3 Mixed amphetamine salts	7	1371	Risk Ratio (M-H, Random, 95% CI)	3.50 [1.86, 6.59]

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Comparison 2. Subgroup analysis 1: comorbidity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician-rated	13		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.04, -0.75]
1.1 With comorbidity	2		Std. Mean Difference (Random, 95% CI)	-0.76 [-1.11, -0.41]
1.2 Without comorbidity	11		Std. Mean Difference (Random, 95% CI)	-0.91 [-1.07, -0.76]
2 ADHD symptom severity: patient-rated	6		Std. Mean Difference (Random, 95% CI)	-0.51 [-0.75, -0.28]
2.1 With comorbidity	1		Std. Mean Difference (Random, 95% CI)	-0.66 [-1.44, 0.12]
2.2 Without comorbidity	5		Std. Mean Difference (Random, 95% CI)	-0.50 [-0.77, -0.23]
3 Retention in treatment	17	2323	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
3.1 With comorbidity	2	158	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.77, 1.33]
3.2 Without comorbidity	15	2165	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.99, 1.15]
4 Proportion of patients withdrawn owing to any adverse event	17	2409	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.64, 4.42]
4.1 With comorbidity	2	158	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.12, 60.93]
4.2 Without comorbidity	15	2251	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.63, 4.45]

Comparison 3. Subgroup analysis 2: type of amphetamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician-rated	13		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.04, -0.75]
1.1 Dexamphetamine	1		Std. Mean Difference (Random, 95% CI)	-0.24 [-0.80, 0.32]
1.2 Lisdexamfetamine	7		Std. Mean Difference (Random, 95% CI)	-1.06 [-1.26, -0.85]
1.3 Mixed amphetamine salts	5		Std. Mean Difference (Random, 95% CI)	-0.80 [-0.93, -0.66]
2 ADHD symptom severity: patient-rated	6		Std. Mean Difference (Random, 95% CI)	-0.51 [-0.75, -0.28]
2.1 Dexamphetamine	2		Std. Mean Difference (Random, 95% CI)	-0.77 [-1.14, -0.40]
2.2 Lisdexamfetamine	3		Std. Mean Difference (Random, 95% CI)	-0.33 [-0.65, -0.01]
2.3 Mixed amphetamine salts	1		Std. Mean Difference (Random, 95% CI)	-0.45 [-1.02, 0.12]
3 Retention in treatment	17	2323	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
3.1 Dexamphetamine	1	49	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.17]
3.2 Lisdexamfetamine	8	873	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
3.3 Mixed amphetamine salts	8	1401	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
4 Proportion of participants withdrawn owing to any adverse event	17	2409	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.64, 4.42]
4.1 Dexamphetamine	1	49	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.31, 9.27]
4.2 Lisdexamfetamine	9	989	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.72, 4.42]
4.3 Mixed amphetamine salts	7	1371	Risk Ratio (M-H, Random, 95% CI)	3.50 [1.86, 6.59]

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Comparison 4. Subgroup analysis 3: dose of dexamphetamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: patient rated	2		Std. Mean Difference (Random, 95% CI)	-0.77 [-1.14, -0.40]
1.1 Lower dose	1		Std. Mean Difference (Random, 95% CI)	-0.55 [-1.10, -0.00]
1.2 Higher dose	1		Std. Mean Difference (Random, 95% CI)	-0.93 [-1.40, -0.46]

Comparison 5. Subgroup analysis 3: dose of lisdexamfetamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	6		Std. Mean Difference (Random, 95% CI)	-1.02 [-1.22, -0.82]
1.1 Lower dose	2		Std. Mean Difference (Random, 95% CI)	-0.98 [-1.41, -0.55]
1.2 Higher dose	5		Std. Mean Difference (Random, 95% CI)	-1.04 [-1.31, -0.78]
2 ADHD symptom severity: patient rated	3		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.61, -0.10]
2.1 Lower dose	1		Std. Mean Difference (Random, 95% CI)	-0.33 [-0.78, 0.12]
2.2 Higher dose	3		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.67, -0.05]
3 Retention in treatment	5	712	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.08]
3.1 Lower dose	2	322	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
3.2 Higher dose	4	390	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
4 Proportion of participants withdrawn owing to any adverse event	6	828	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.09, 6.75]
4.1 Lower dose	3	335	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.56, 15.72]
4.2 Higher dose	4	493	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.88, 7.75]

Comparison 6. Subgroup analysis 3: dose of mixed amphetamine salts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	5		Std. Mean Difference (Random, 95% CI)	-0.81 [-0.94, -0.69]
1.1 Lower dose	3		Std. Mean Difference (Random, 95% CI)	-0.78 [-0.94, -0.63]
1.2 Higher dose	3		Std. Mean Difference (Random, 95% CI)	-0.86 [-1.06, -0.66]
2 Retention in treatment	8	1569	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.05, 1.28]
2.1 Lower dose (50 mg/d)	5	962	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.96, 1.32]
2.2 Higher dose (50 mg/d)	5	607	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.09, 1.35]

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3 Proportion of participants withdrawn owing to any adverse event	7	1539	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.16, 6.44]
3.1 Lower dose	5	962	Risk Ratio (M-H, Random, 95% CI)	3.59 [1.84, 7.00]
3.2 Higher dose	4	577	Risk Ratio (M-H, Random, 95% CI)	4.03 [1.56, 10.42]

Comparison 7. Subgroup analysis 4: type of drug-release formulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	13		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.04, -0.75]
1.1 Immediate-release formulations	1		Std. Mean Difference (Random, 95% CI)	-0.91 [-1.38, -0.44]
1.2 Sustained-release formulations	12		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.05, -0.74]
2 ADHD symptom severity: patient rated	6		Std. Mean Difference (Random, 95% CI)	-0.51 [-0.75, -0.27]
2.1 Immediate-release formulations	3		Std. Mean Difference (Random, 95% CI)	-0.67 [-0.98, -0.37]
2.2 Sustained-release formulations	3		Std. Mean Difference (Random, 95% CI)	-0.33 [-0.65, -0.01]
3 Retention in treatment	17	2323	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
3.1 Immediate-release formulations	2	41	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.40]
3.2 Sustained-release formulations	15	2282	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.13]

Comparison 8. Sensitivity analysis: incomplete subjective outcome data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	1		Std. Mean Difference (Random, 95% CI)	Totals not selected
2 ADHD symptom severity: patient rated	2		Std. Mean Difference (Random, 95% CI)	-0.77 [-1.14, -0.40]

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Comparison 9. Sensitivity analysis: other potential sources of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	9		Std. Mean Difference (Random, 95% CI)	-0.84 [-1.02, -0.66]
2 ADHD symptom severity: patient rated	3		Std. Mean Difference (Random, 95% CI)	-0.75 [-1.07, -0.43]
3 Retention in treatment	9	1661	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.13]

Comparison 10. Sensitivity analysis: fixed-effect model

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician-rated	13		Std. Mean Difference (Fixed, 95% CI)	-0.89 [-0.98, -0.79]
1.1 Dexamphetamine	1		Std. Mean Difference (Fixed, 95% CI)	-0.24 [-0.80, 0.32]
1.2 Lisdexamfetamine	7		Std. Mean Difference (Fixed, 95% CI)	-1.04 [-1.19, -0.90]
1.3 Mixed amphetamine salts	5		Std. Mean Difference (Fixed, 95% CI)	-0.80 [-0.93, -0.66]
2 ADHD symptom severity: patient-rated	6		Std. Mean Difference (Fixed, 95% CI)	-0.51 [-0.73, -0.29]
2.1 Dexamphetamine	2		Std. Mean Difference (Fixed, 95% CI)	-0.77 [-1.13, -0.41]
2.2 Lisdexamfetamine	3		Std. Mean Difference (Fixed, 95% CI)	-0.33 [-0.65, -0.01]
2.3 Mixed amphetamine salts	1		Std. Mean Difference (Fixed, 95% CI)	-0.45 [-1.02, 0.12]
3 Clinical impression of severity at study end	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-1.09 [-1.57, -0.61]
4 Clinical impression of improvement at study end	1	263	Std. Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.01, -0.48]
5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms	2	381	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.18, 1.95]
6 Proportion of participants achieving a CGI-Improvement score of 1 or 2	8	1707	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [2.14, 2.97]
7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.34, 4.82]
8 Global functioning	2	110	Std. Mean Difference (IV, Fixed, 95% CI)	0.56 [0.17, 0.95]
9 Depressive symptoms	2	110	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.22, 0.53]
10 Anxiety symptoms	2	110	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.24, 0.51]
11 Retention in treatment	17	2323	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.04, 1.16]
11.1 Dexamphetamine	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.17]
11.2 Lisdexamfetamine	8	873	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.11]

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11.3 Mixed amphetamine salts	8	1401	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.07, 1.24]
12 Proportion of participants withdrawn owing to any cardiovascular adverse event	2	675	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.32, 19.54]
13 Proportion of participants withdrawn owing to any adverse event	17	2409	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [1.86, 4.83]
13.1 Dexamphetamine	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.31, 9.27]
13.2 Lisdexamfetamine	9	989	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.78, 4.02]
13.3 Mixed amphetamine salts	7	1371	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [2.14, 7.67]

Comparison 11. Post hoc sensitivity analysis 1: calculation of effect sizes using correlation coefficient from Taylor 2000

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	13		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.05, -0.76]
2 ADHD symptom severity: patient rated	6		Std. Mean Difference (Random, 95% CI)	-0.47 [-0.69, -0.25]

Comparison 12. Post hoc sensitivity analysis 2: pooled risk difference for proportion of participants withdrawn owing to cardiovascular adverse events and any adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants withdrawn owing to any cardiovascular adverse event	3	699	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.00, 0.04]
2 Proportion of participants withdrawn owing to any adverse event	17	2409	Risk Difference (M-H, Random, 95% CI)	0.04 [0.01, 0.06]
2.1 Dexamphetamine	1	49	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.12, 0.23]
2.2 Lisdexamfetamine	9	989	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
2.3 Mixed amphetamine salts	7	1371	Risk Difference (M-H, Random, 95% CI)	0.06 [0.02, 0.10]

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Comparison 13. Post hoc sensitivity analysis 3: exclusion of cross-over study

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	12		Std. Mean Difference (Random, 95% CI)	-0.90 [-1.05, -0.74]

Comparison 14. Amphetamines vs guanfacine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: patient rated	1		Std. Mean Difference (Random, 95% CI)	Totals not selected

Comparison 15. Amphetamines vs modafinil for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: patient rated	1		Std. Mean Difference (Random, 95% CI)	Totals not selected

Comparison 16. Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADHD symptom severity: clinician rated	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Proportion of participants achieving a CGI-Improvement score of 1 or 2	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Global functioning	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Depressive symptoms	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Anxiety symptoms	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Retention in treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Proportion of participants withdrawn owing to any adverse event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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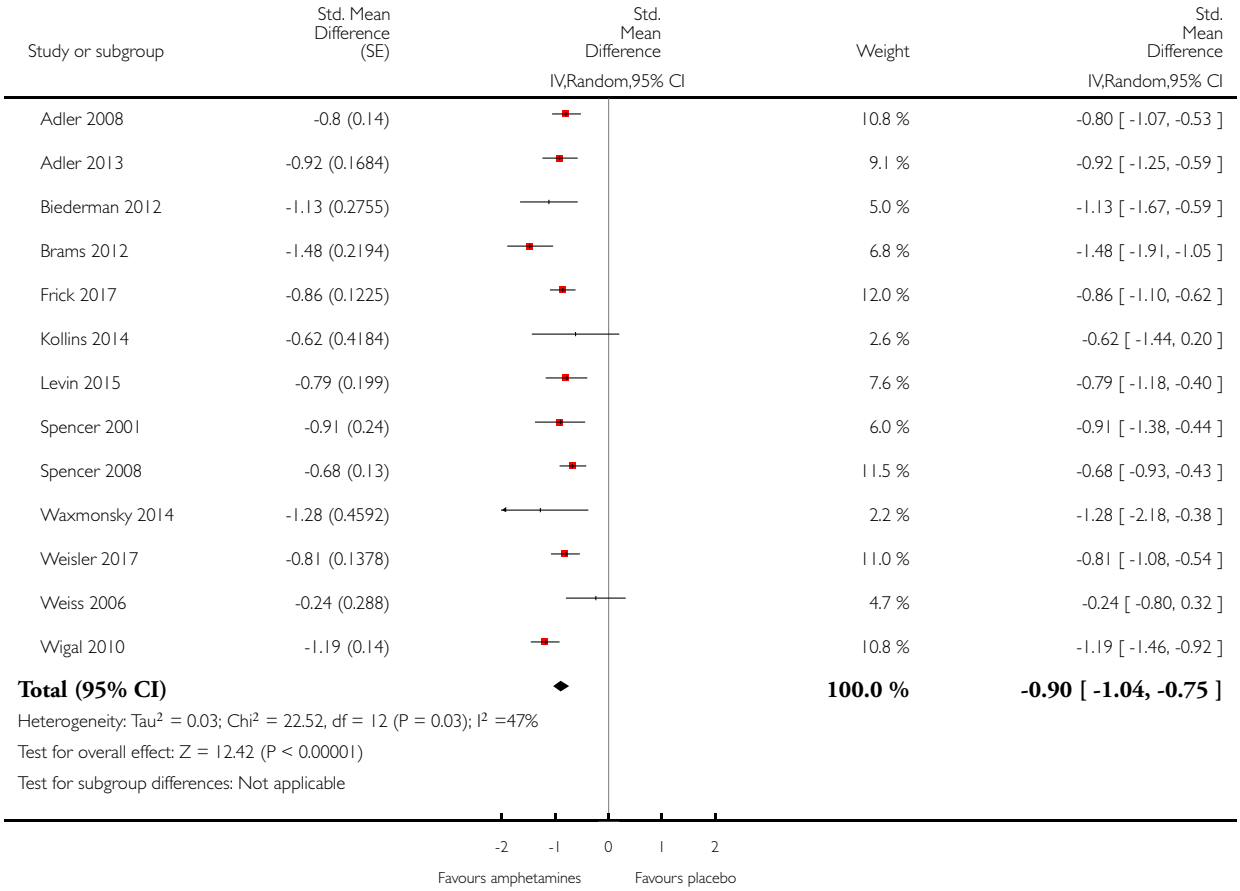
Analysis 1.1. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 1 ADHD symptom severity: clinician-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 1 ADHD symptom severity: clinician-rated



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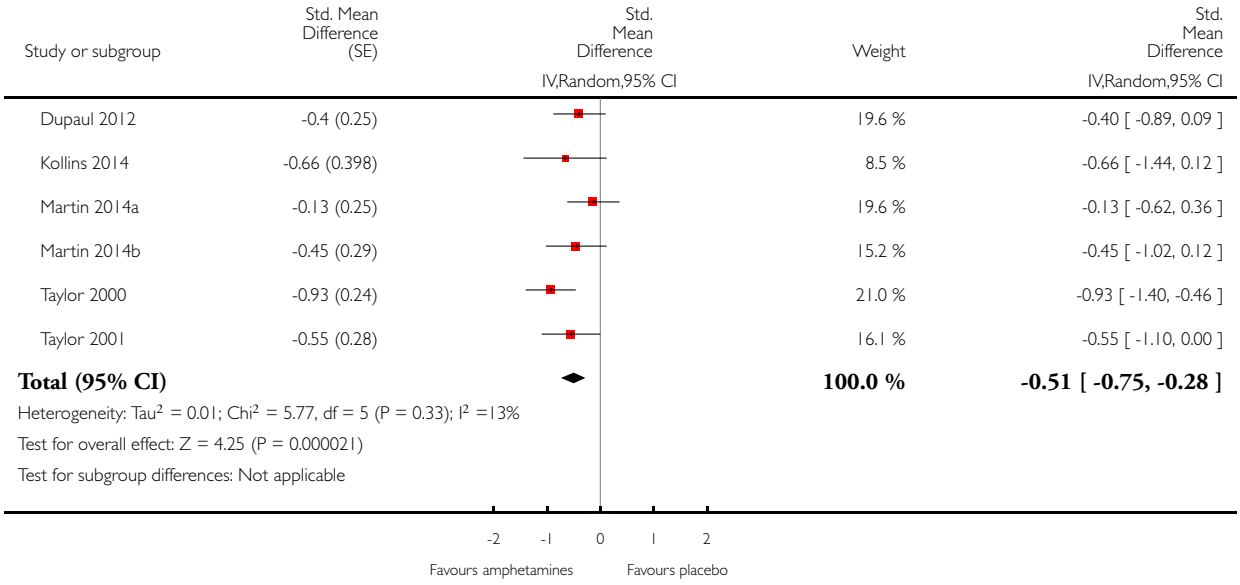
Analysis 1.2. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 2 ADHD symptom severity: patient-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 2 ADHD symptom severity: patient-rated



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Analysis 1.3. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 3 Clinical impression of severity at study end.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 3 Clinical impression of severity at study end

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Spencer 2001	27	3.4 (1)	27	4.4 (0.9)		70.7 %	-1.04 [-1.61, -0.47]
Waxmonsky 2014	11	1.36 (0.81)	13	2.38 (0.81)		29.3 %	-1.22 [-2.10, -0.33]
Total (95% CI)	**38**		**40**			**100.0 %**	**-1.09 [-1.57, -0.61]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 4 Clinical impression of improvement at study end.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 4 Clinical impression of improvement at study end

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Weisler 2017	177	2.2 (1.27)	86	3.1 (1.05)		100.0 %	-0.75 [-1.01, -0.48]
Total (95% CI)	**177**		**86**			**100.0 %**	**-0.75 [-1.01, -0.48]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.51 (P < 0.00001)

Test for subgroup differences: Not applicable

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Analysis 1.5. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms

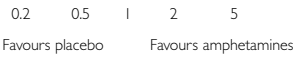
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Levin 2015	55/83	17/43		39.0 %	1.68 [1.12, 2.50]
Weisler 2006	111/191	26/64		61.0 %	1.43 [1.04, 1.97]
Total (95% CI)	**274**	**107**		**100.0 %**	**1.52 [1.19, 1.95]**

Total events: 166 (Amphetamines), 43 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 3.29 (P = 0.00099)

Test for subgroup differences: Not applicable



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Analysis 1.6. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 6 Proportion of participants achieving a CGI-Improvement score of 1 or 2.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 6 Proportion of participants achieving a CGI-Improvement score of 1 or 2

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Adler 2008	206/358	18/62		16.5 %	1.98 [1.33, 2.95]
Adler 2013	62/79	26/75		23.9 %	2.26 [1.63, 3.15]
Frick 2017	197/302	21/103		17.2 %	3.20 [2.17, 4.73]
Levin 2015	31/83	5/43		3.5 %	3.21 [1.35, 7.67]
Spencer 2008	70/137	28/137		19.3 %	2.50 [1.73, 3.61]
Waxmonsky 2014	9/11	4/13		3.5 %	2.66 [1.12, 6.29]
Weisler 2006	103/191	16/64		13.3 %	2.16 [1.38, 3.36]
Weiss 2006	15/23	4/26		2.9 %	4.24 [1.64, 10.96]
Total (95% CI)	**1184**	**523**		**100.0 %**	**2.47 [2.10, 2.90]**
Total events: 693 (Amphetamines), 122 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.17, df = 7 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 10.94 (P < 0.00001)					
Test for subgroup differences: Not applicable					

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Analysis 1.7. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Biederman 2012	21/31	8/30		100.0 %	2.54 [1.34, 4.82]
Total (95% CI)	**31**	**30**		**100.0 %**	**2.54 [1.34, 4.82]**
Total events: 21 (Amphetamines), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.85 (P = 0.0044)					
Test for subgroup differences: Not applicable					

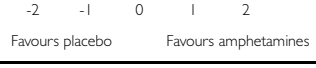
Analysis 1.8. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 8 Global functioning.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 8 Global functioning

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Biederman 2012	31	63.5 (4.4)	30	58.9 (4.8)		50.5 %	0.99 [0.45, 1.52]
Weiss 2006	23	60 (15.89)	26	58.88 (9.84)		49.5 %	0.08 [-0.48, 0.65]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.54 [-0.34, 1.42]**
Heterogeneity: Tau^2 = 0.33; Chi^2 = 5.22, df = 1 (P = 0.02); I^2 =81%							
Test for overall effect: Z = 1.20 (P = 0.23)							
Test for subgroup differences: Not applicable							



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Analysis 1.9. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 9 Depressive symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 9 Depressive symptoms

Study or subgroup	Amphetamines		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Biederman 2012	31	1.3 (1.7)	30	1.2 (1.6)		55.8 %	0.06 [-0.44, 0.56]
Weiss 2006	23	7.56 (7.25)	26	6 (3.29)		44.2 %	0.28 [-0.29, 0.84]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.16 [-0.22, 0.53]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

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Analysis 1.10. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 10 Anxiety symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

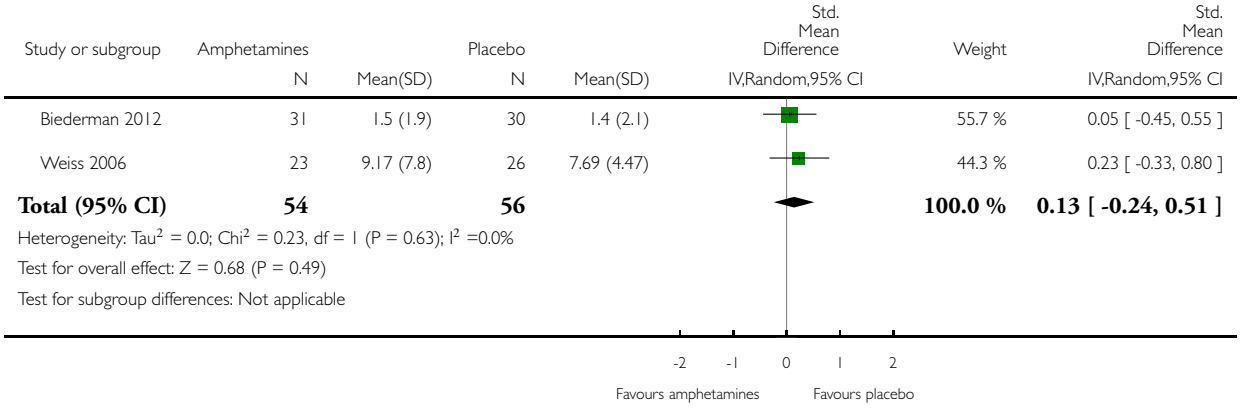
Outcome: 10 Anxiety symptoms

Study or subgroup	Amphetamines		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Biederman 2012	31	1.5 (1.9)	30	1.4 (2.1)		55.7 %	0.05 [-0.45, 0.55]
Weiss 2006	23	9.17 (7.8)	26	7.69 (4.47)		44.3 %	0.23 [-0.33, 0.80]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.13 [-0.24, 0.51]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 0.68 (P = 0.49)

Test for subgroup differences: Not applicable



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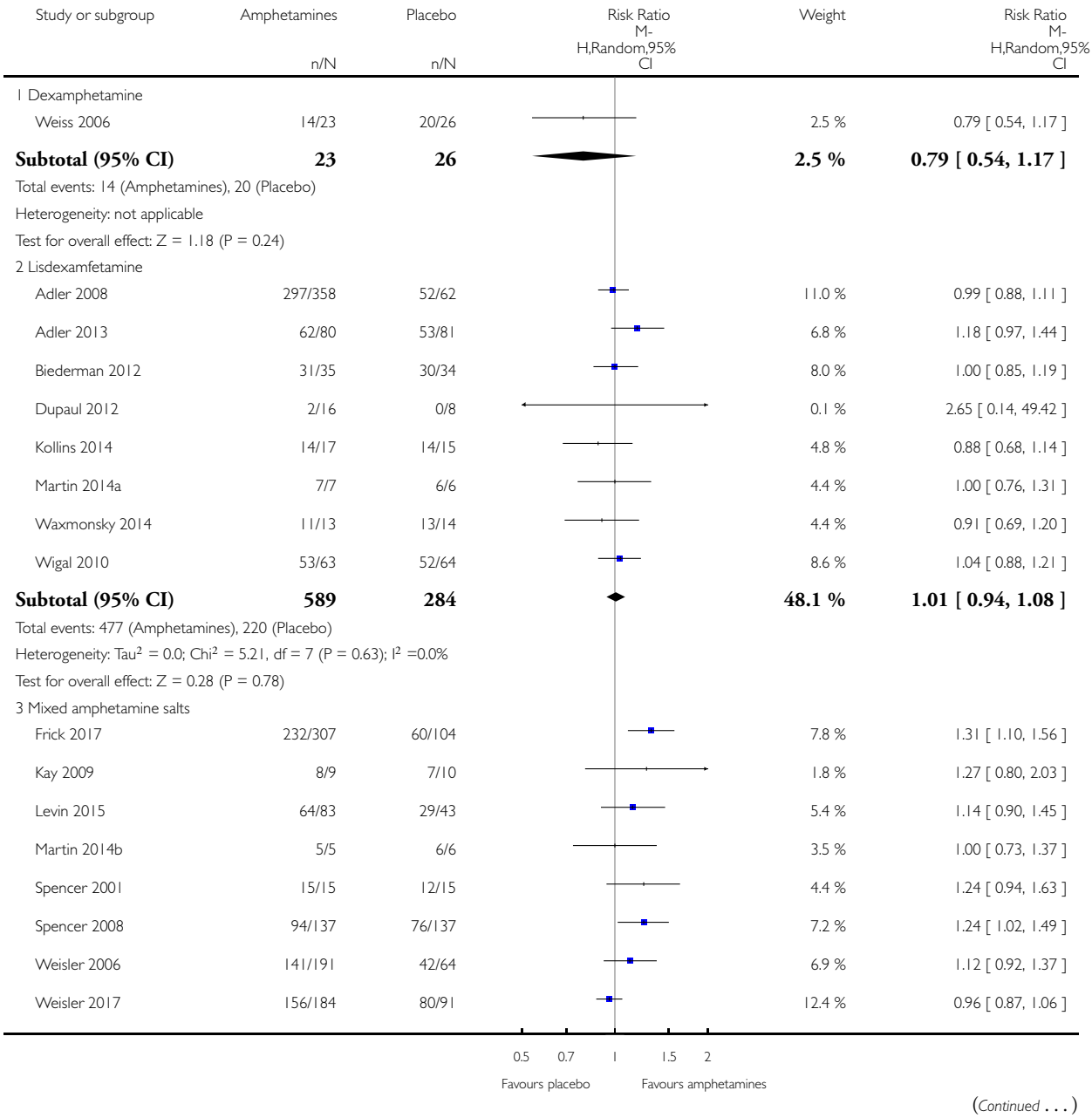
Analysis 1.11. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 11 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 11 Retention in treatment



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Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**931**	**470**		**49.3 %**	**1.14 [1.02, 1.28]**
Total events: 715 (Amphetamines), 312 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 16.44, df = 7 (P = 0.02); I^2 =57%					
Test for overall effect: Z = 2.25 (P = 0.024)					
Total (95% CI)	**1543**	**780**		**100.0 %**	**1.06 [0.99, 1.13]**
Total events: 1206 (Amphetamines), 552 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 26.69, df = 16 (P = 0.05); I^2 =40%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi^2 = 5.07, df = 2 (P = 0.08), I^2 =61%					

Analysis 1.12. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 12 Proportion of participants withdrawn owing to any cardiovascular adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 12 Proportion of participants withdrawn owing to any cardiovascular adverse event

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Adler 2008	7/358	0/62		36.0 %	2.63 [0.15, 45.51]
Dupaul 2012	1/16	0/8		30.5 %	1.59 [0.07, 35.15]
Weisler 2006	3/191	0/64		33.6 %	2.37 [0.12, 45.27]
Total (95% CI)	**565**	**134**		**100.0 %**	**2.18 [0.39, 12.04]**
Total events: 11 (Amphetamines), 0 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 2 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 0.89 (P = 0.37)					
Test for subgroup differences: Not applicable					

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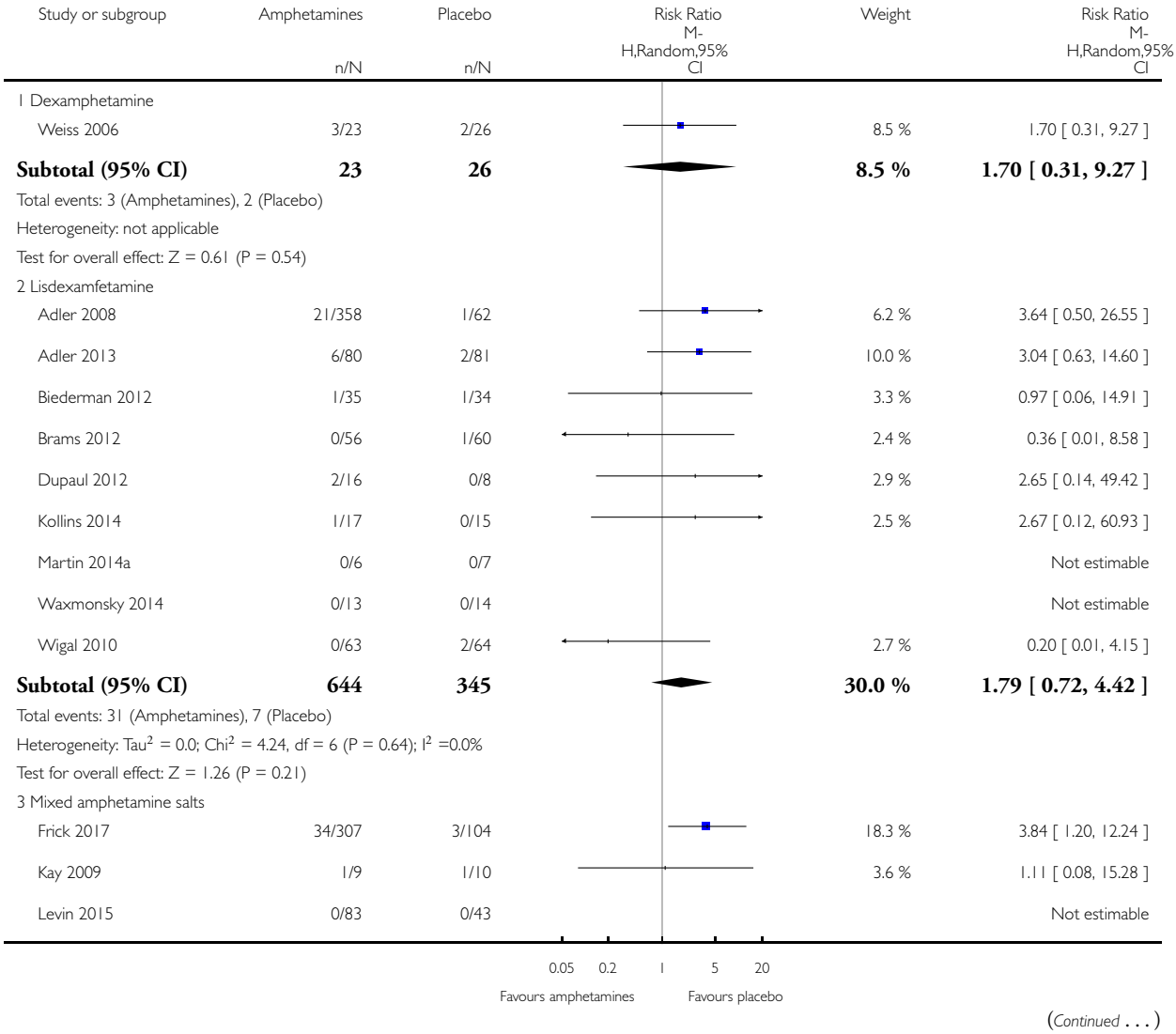
Analysis 1.13. Comparison 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 13 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Amphetamines vs placebo for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 13 Proportion of participants withdrawn owing to any adverse event



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Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Martin 2014b	0/6	0/5			Not estimable
Spencer 2008	17/137	6/137		30.3 %	2.83 [1.15, 6.97]
Weisler 2006	23/191	1/64		6.3 %	7.71 [1.06, 55.93]
Weisler 2017	12/184	0/91		3.1 %	12.43 [0.74, 207.67]
Subtotal (95% CI)	**917**	**454**		**61.5 %**	**3.50 [1.86, 6.59]**
Total events: 87 (Amphetamines), 11 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.57$, df = 4 (P = 0.63); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.89 (P = 0.00010)					
Total (95% CI)	**1584**	**825**		**100.0 %**	**2.69 [1.64, 4.42]**
Total events: 121 (Amphetamines), 20 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.50$, df = 12 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.92 (P = 0.000090)					
Test for subgroup differences: $Chi^2 = 1.73$, df = 2 (P = 0.42), $I^2 = 0.0\%$					

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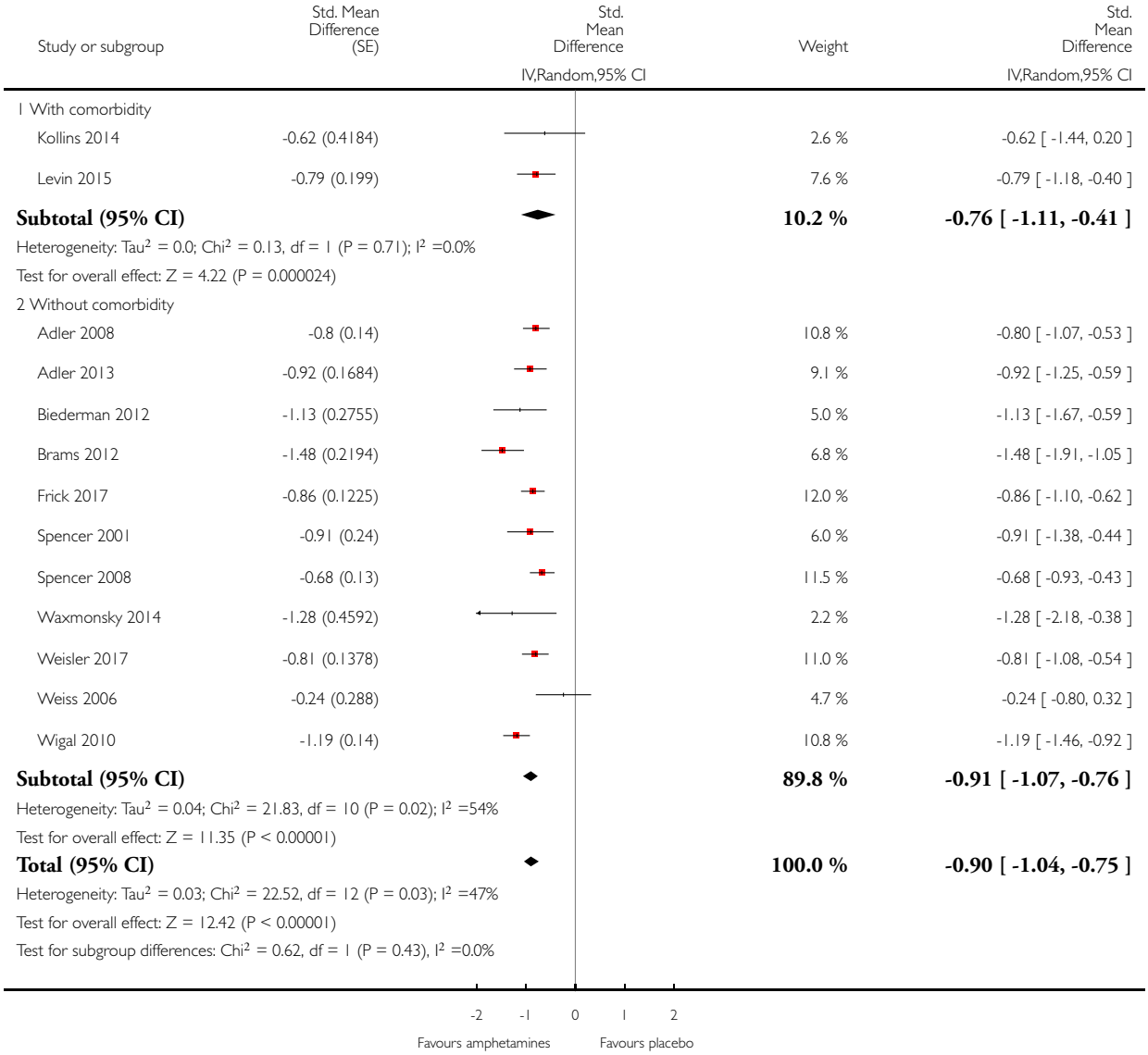
Analysis 2.1. Comparison 2 Subgroup analysis 1: comorbidity, Outcome 1 ADHD symptom severity: clinician-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 2 Subgroup analysis 1: comorbidity

Outcome: 1 ADHD symptom severity: clinician-rated



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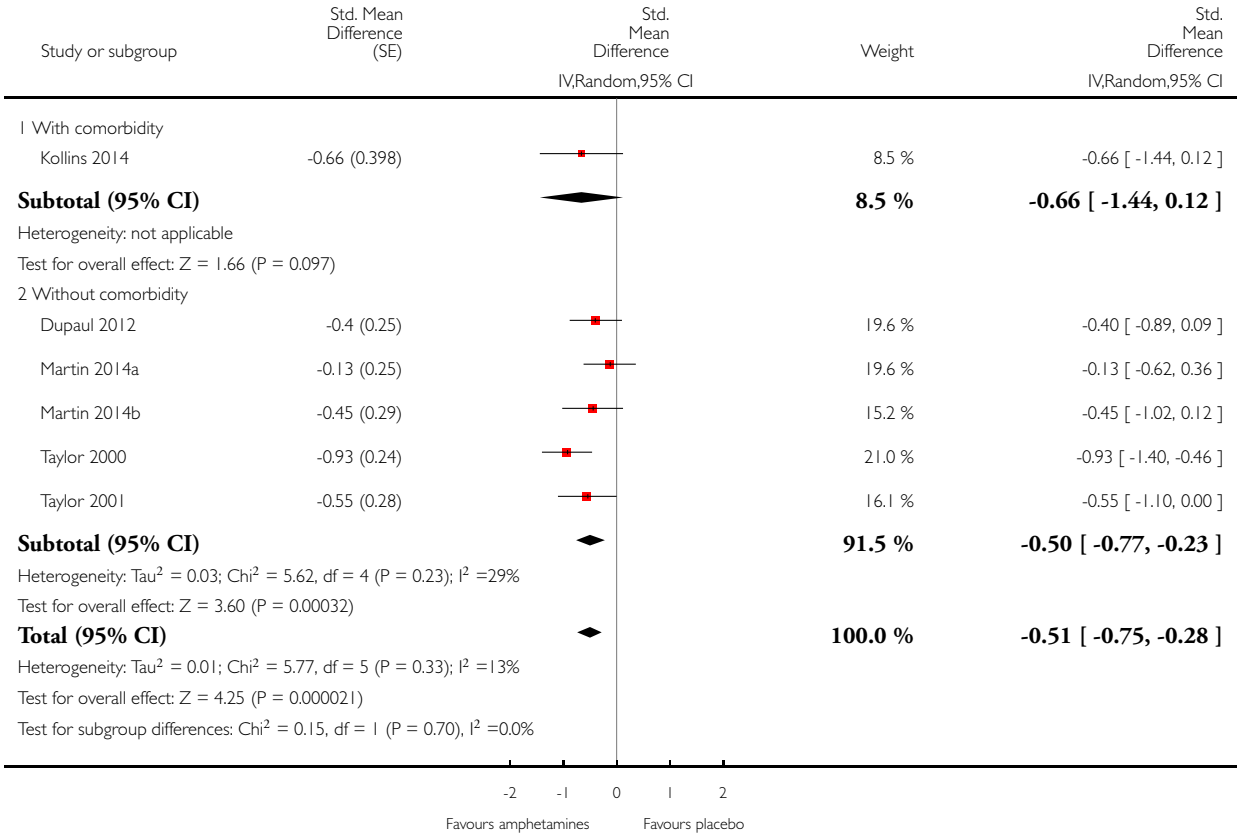
Analysis 2.2. Comparison 2 Subgroup analysis 1: comorbidity, Outcome 2 ADHD symptom severity: patient-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 2 Subgroup analysis 1: comorbidity

Outcome: 2 ADHD symptom severity: patient-rated



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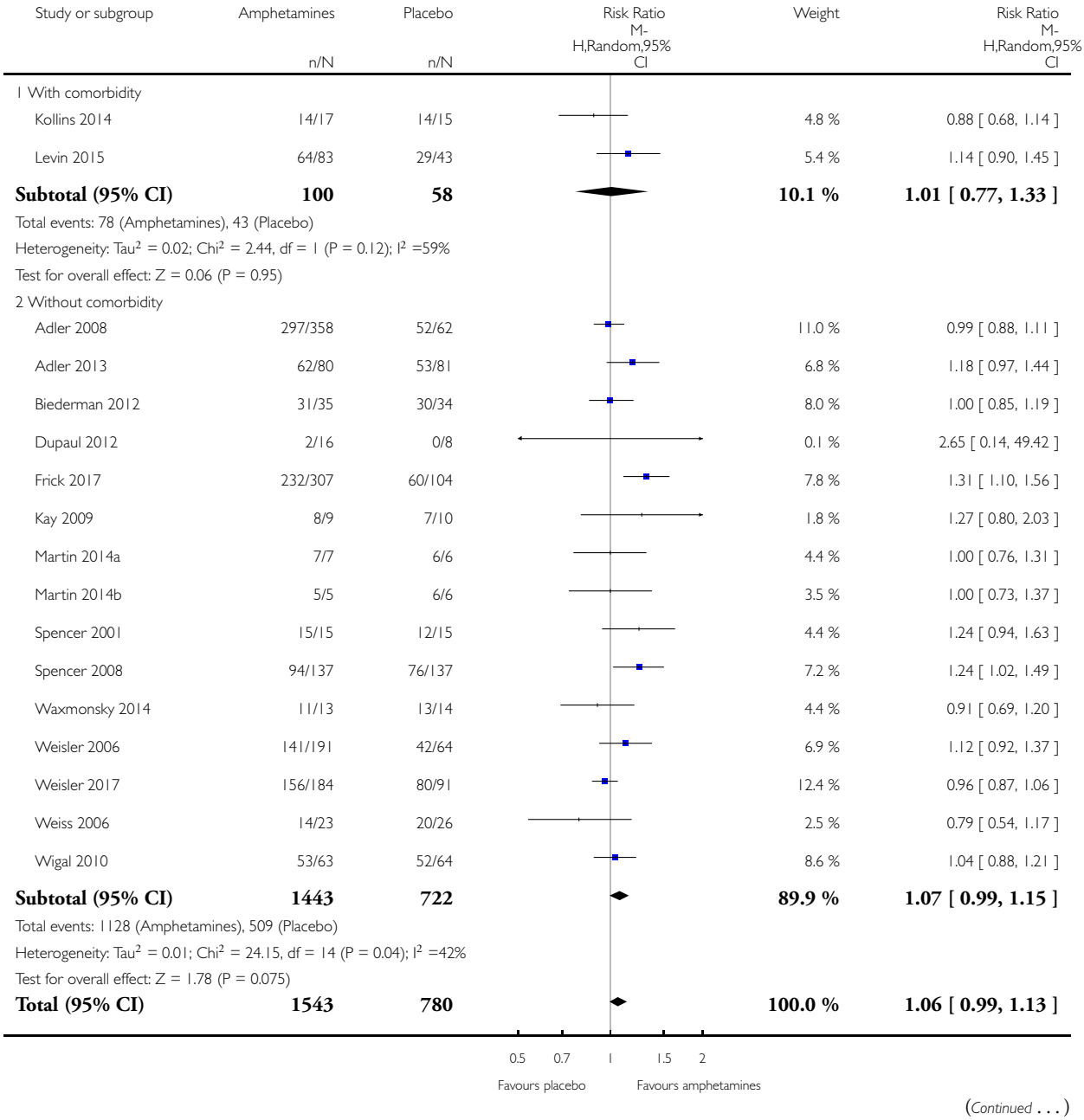
Analysis 2.3. Comparison 2 Subgroup analysis 1: comorbidity, Outcome 3 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 2 Subgroup analysis 1: comorbidity

Outcome: 3 Retention in treatment



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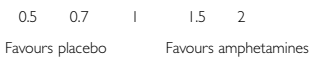
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 1206 (Amphetamines), 552 (Placebo)					
Heterogeneity: Tau² = 0.01; Chi² = 26.69, df = 16 (P = 0.05); I² =40%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² =0.0%					



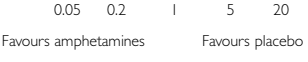
Analysis 2.4. Comparison 2 Subgroup analysis 1: comorbidity, Outcome 4 Proportion of patients withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 2 Subgroup analysis 1: comorbidity

Outcome: 4 Proportion of patients withdrawn owing to any adverse event

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 With comorbidity					
Kollins 2014	1/17	0/15		2.5 %	2.67 [0.12, 60.93]
Levin 2015	0/83	0/43			Not estimable
Subtotal (95% CI)	**100**	**58**		**2.5 %**	**2.67 [0.12, 60.93]**
Total events: 1 (Amphetamines), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Without comorbidity					
Adler 2008	21/358	1/62		6.2 %	3.64 [0.50, 26.55]
Adler 2013	6/80	2/81		10.0 %	3.04 [0.63, 14.60]
Biederman 2012	1/35	1/34		3.3 %	0.97 [0.06, 14.91]
Brams 2012	0/56	1/60		2.4 %	0.36 [0.01, 8.58]
Dupaul 2012	2/16	0/8		2.9 %	2.65 [0.14, 49.42]



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Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Frick 2017	34/307	3/104		18.3 %	3.84 [1.20, 12.24]
Kay 2009	1/9	1/10		3.6 %	1.11 [0.08, 15.28]
Martin 2014a	0/6	0/7			Not estimable
Martin 2014b	0/6	0/5			Not estimable
Spencer 2008	17/137	6/137		30.3 %	2.83 [1.15, 6.97]
Waxmonsky 2014	0/13	0/14			Not estimable
Weisler 2006	23/191	1/64		6.3 %	7.71 [1.06, 55.93]
Weisler 2017	12/184	0/91		3.1 %	12.43 [0.74, 207.67]
Weiss 2006	3/23	2/26		8.5 %	1.70 [0.31, 9.27]
Wigal 2010	0/63	2/64		2.7 %	0.20 [0.01, 4.15]
Subtotal (95% CI)	**1484**	**767**		**97.5 %**	**2.69 [1.63, 4.45]**
Total events: 120 (Amphetamines), 20 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.50, df = 11 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 3.87 (P = 0.00011)					
Total (95% CI)	**1584**	**825**		**100.0 %**	**2.69 [1.64, 4.42]**
Total events: 121 (Amphetamines), 20 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.50, df = 12 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 3.92 (P = 0.000090)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 =0.0%					

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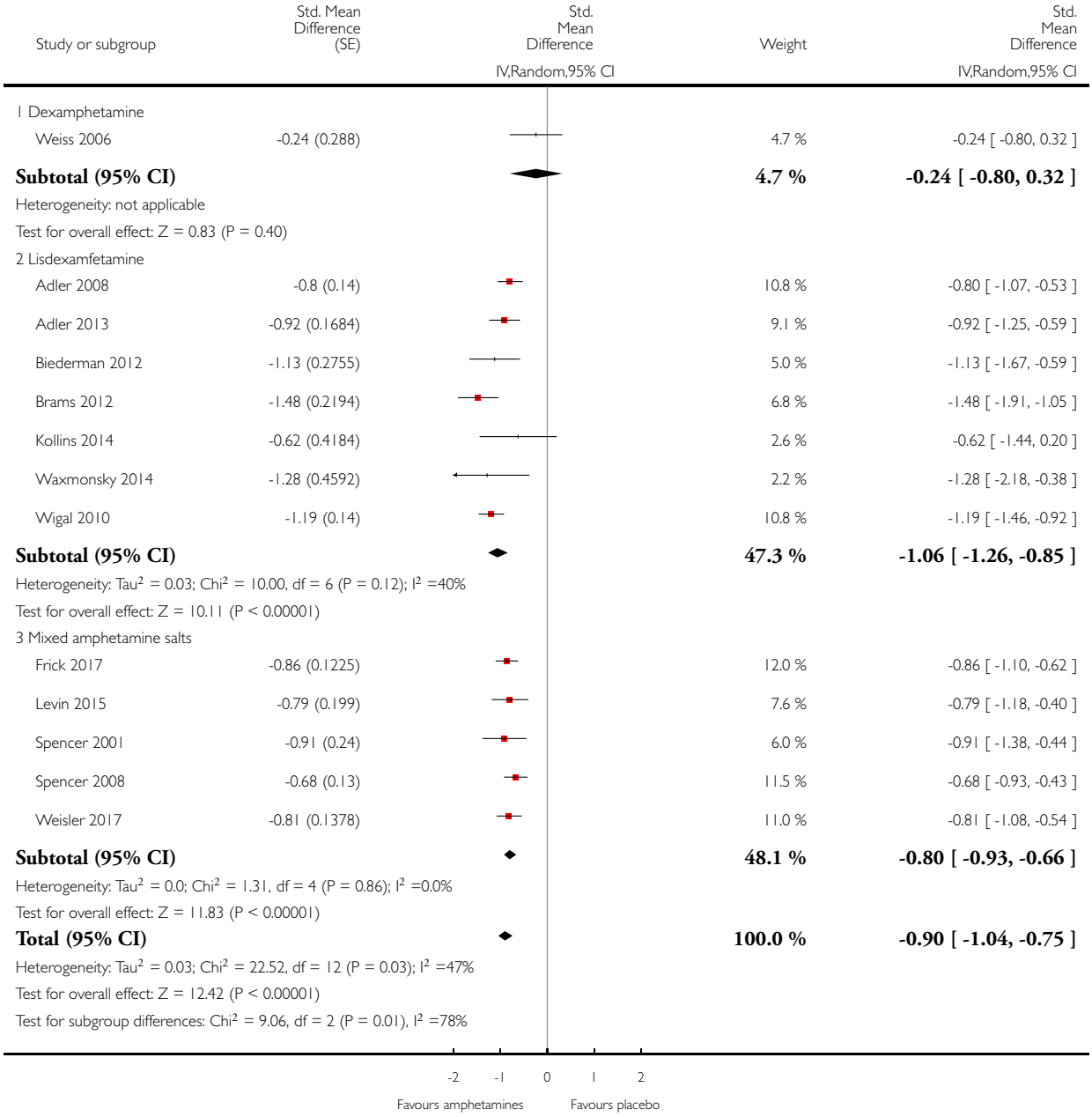
Analysis 3.1. Comparison 3 Subgroup analysis 2: type of amphetamine, Outcome 1 ADHD symptom severity: clinician-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 3 Subgroup analysis 2: type of amphetamine

Outcome: 1 ADHD symptom severity: clinician-rated



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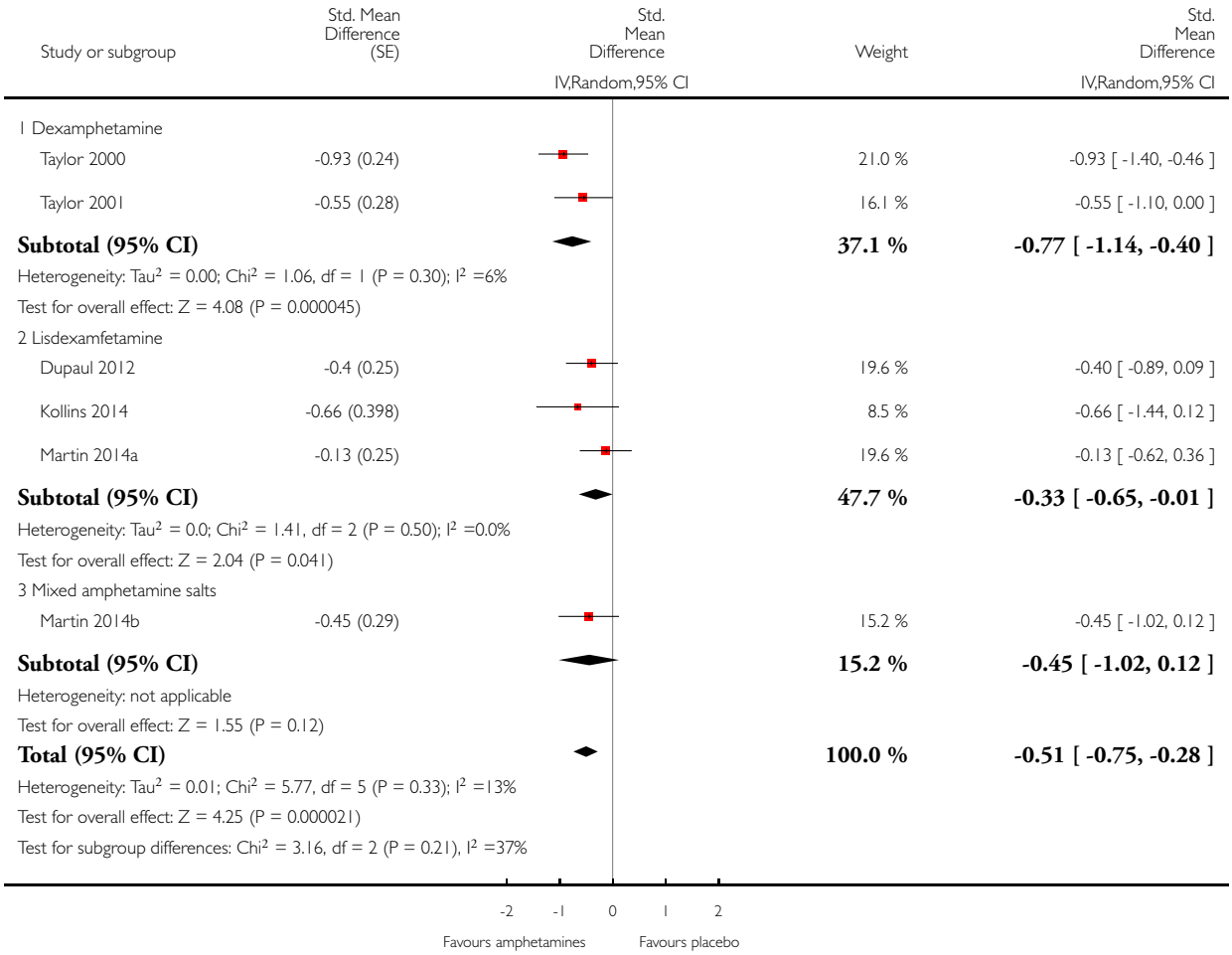
Analysis 3.2. Comparison 3 Subgroup analysis 2: type of amphetamine, Outcome 2 ADHD symptom severity: patient-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 3 Subgroup analysis 2: type of amphetamine

Outcome: 2 ADHD symptom severity: patient-rated



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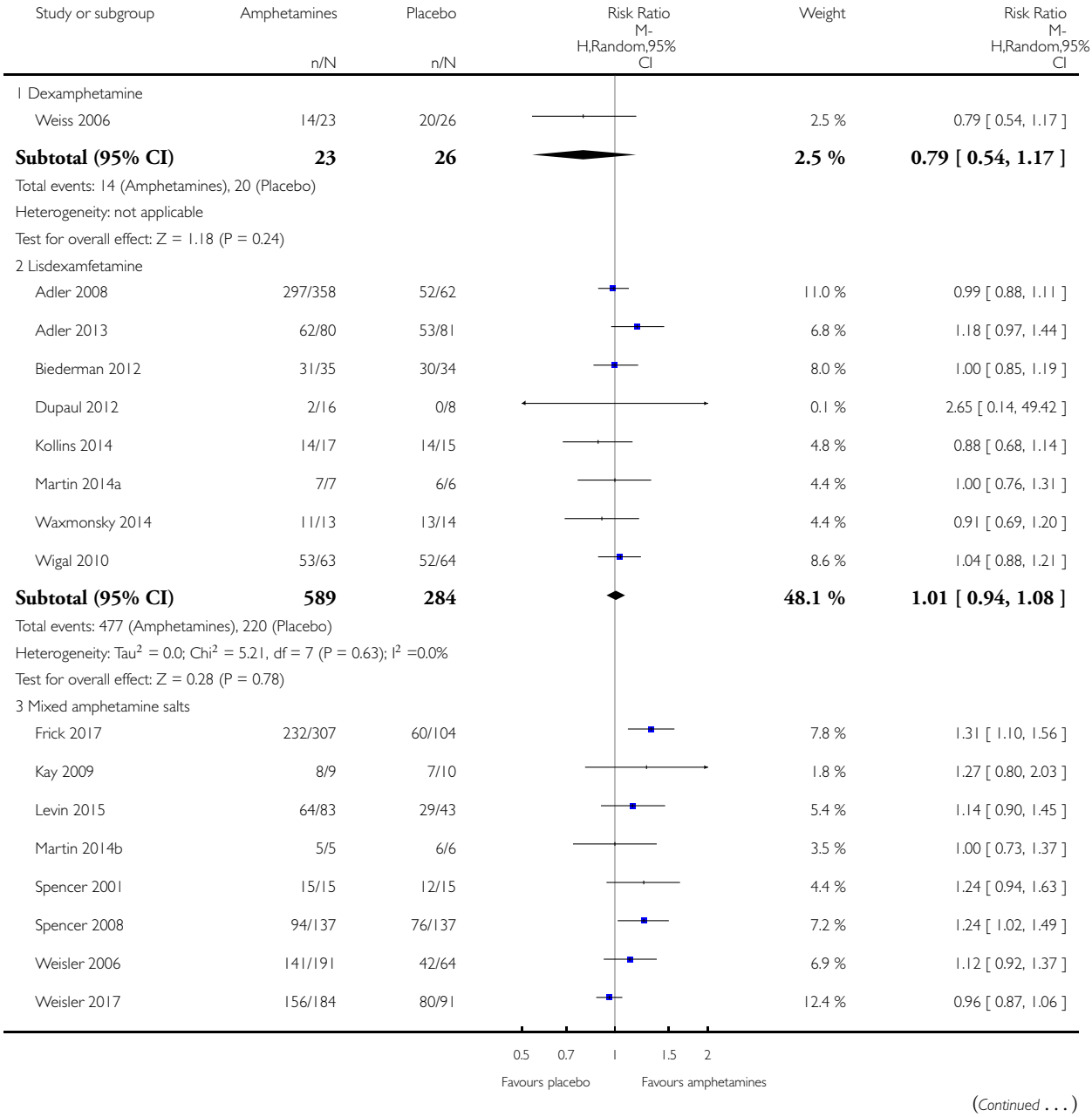
Analysis 3.3. Comparison 3 Subgroup analysis 2: type of amphetamine, Outcome 3 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 3 Subgroup analysis 2: type of amphetamine

Outcome: 3 Retention in treatment



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Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**931**	**470**		**49.3 %**	**1.14 [1.02, 1.28]**
Total events: 715 (Amphetamines), 312 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 16.44, df = 7 (P = 0.02); I^2 =57%					
Test for overall effect: Z = 2.25 (P = 0.024)					
Total (95% CI)	**1543**	**780**		**100.0 %**	**1.06 [0.99, 1.13]**
Total events: 1206 (Amphetamines), 552 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 26.69, df = 16 (P = 0.05); I^2 =40%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi^2 = 5.07, df = 2 (P = 0.08), I^2 =61%					

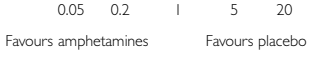
Analysis 3.4. Comparison 3 Subgroup analysis 2: type of amphetamine, Outcome 4 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 3 Subgroup analysis 2: type of amphetamine

Outcome: 4 Proportion of participants withdrawn owing to any adverse event

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dexamphetamine					
Weiss 2006	3/23	2/26		8.5 %	1.70 [0.31, 9.27]
Subtotal (95% CI)	**23**	**26**		**8.5 %**	**1.70 [0.31, 9.27]**
Total events: 3 (Amphetamines), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Lisdexamfetamine					
Adler 2008	21/358	1/62		6.2 %	3.64 [0.50, 26.55]
Adler 2013	6/80	2/81		10.0 %	3.04 [0.63, 14.60]
Biederman 2012	1/35	1/34		3.3 %	0.97 [0.06, 14.91]



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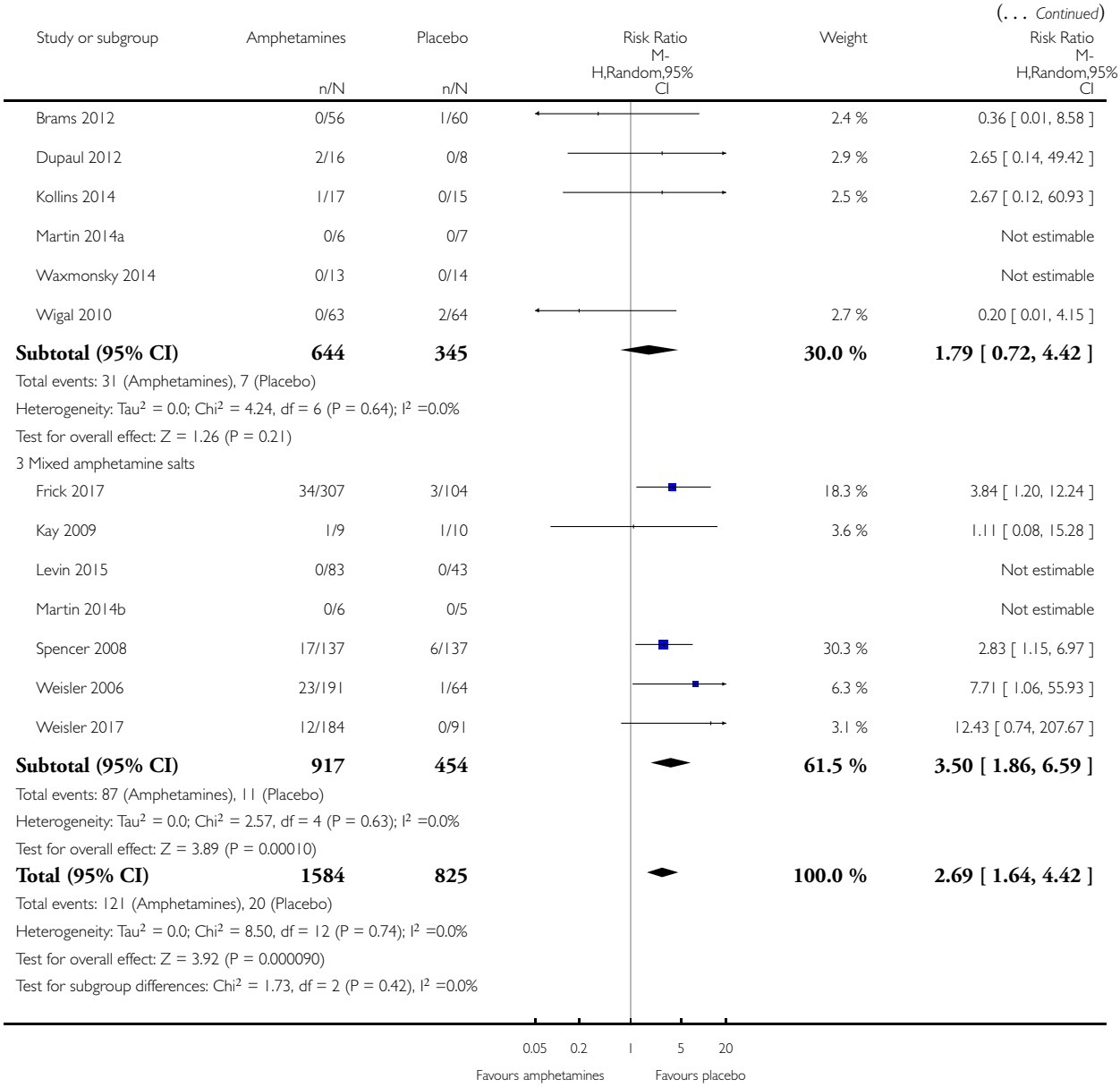

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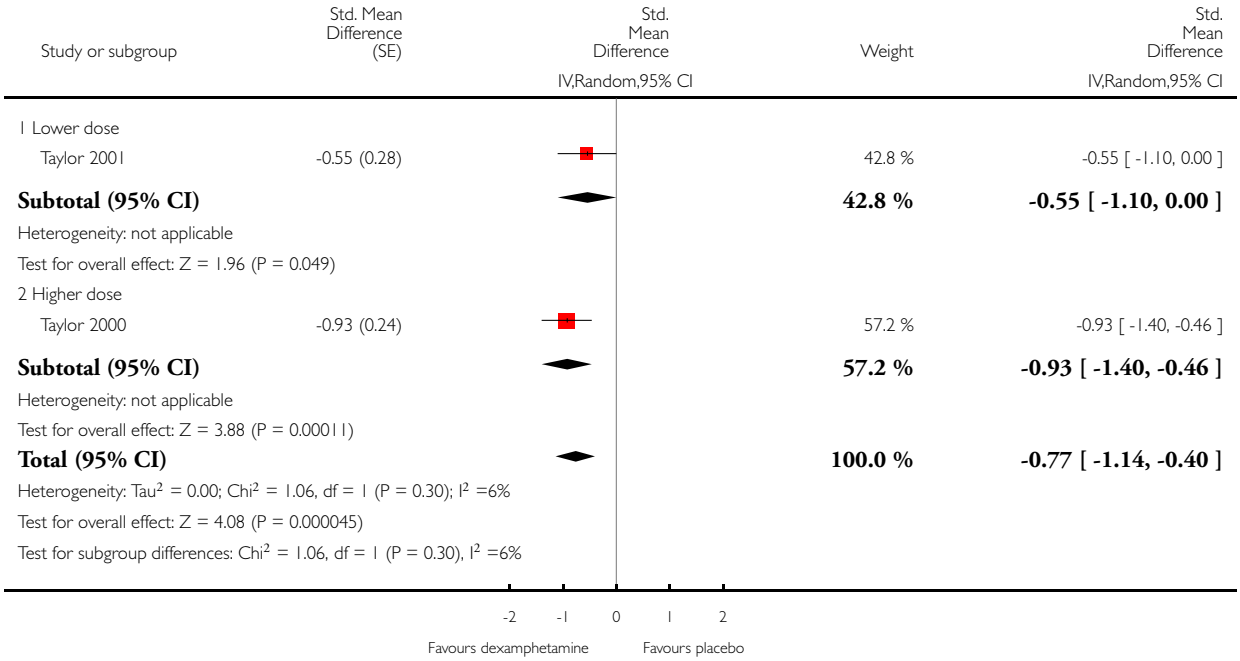
Analysis 4.1. Comparison 4 Subgroup analysis 3: dose of dexamphetamine, Outcome 1 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 4 Subgroup analysis 3: dose of dexamphetamine

Outcome: 1 ADHD symptom severity: patient rated



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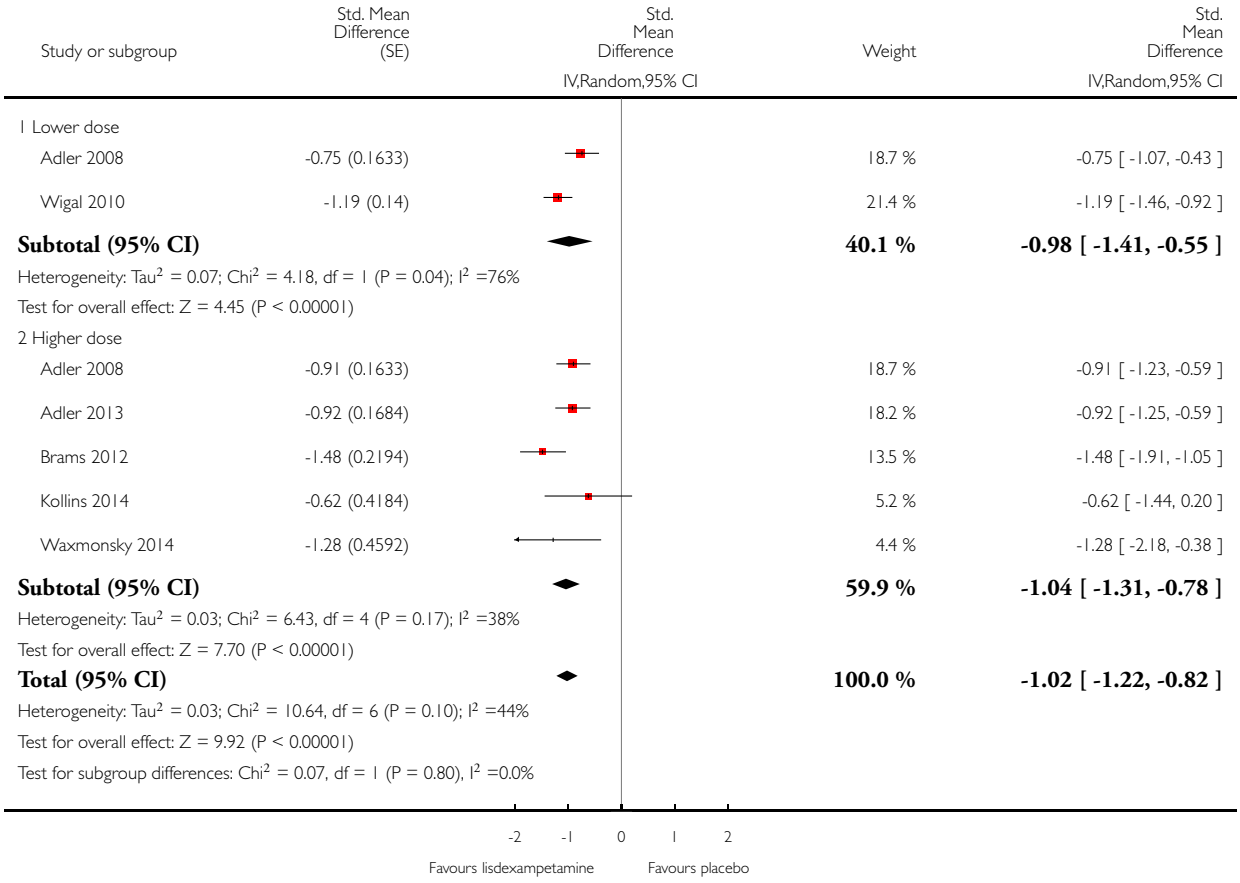
Analysis 5.1. Comparison 5 Subgroup analysis 3: dose of lisdexamfetamine, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 5 Subgroup analysis 3: dose of lisdexamfetamine

Outcome: 1 ADHD symptom severity: clinician rated



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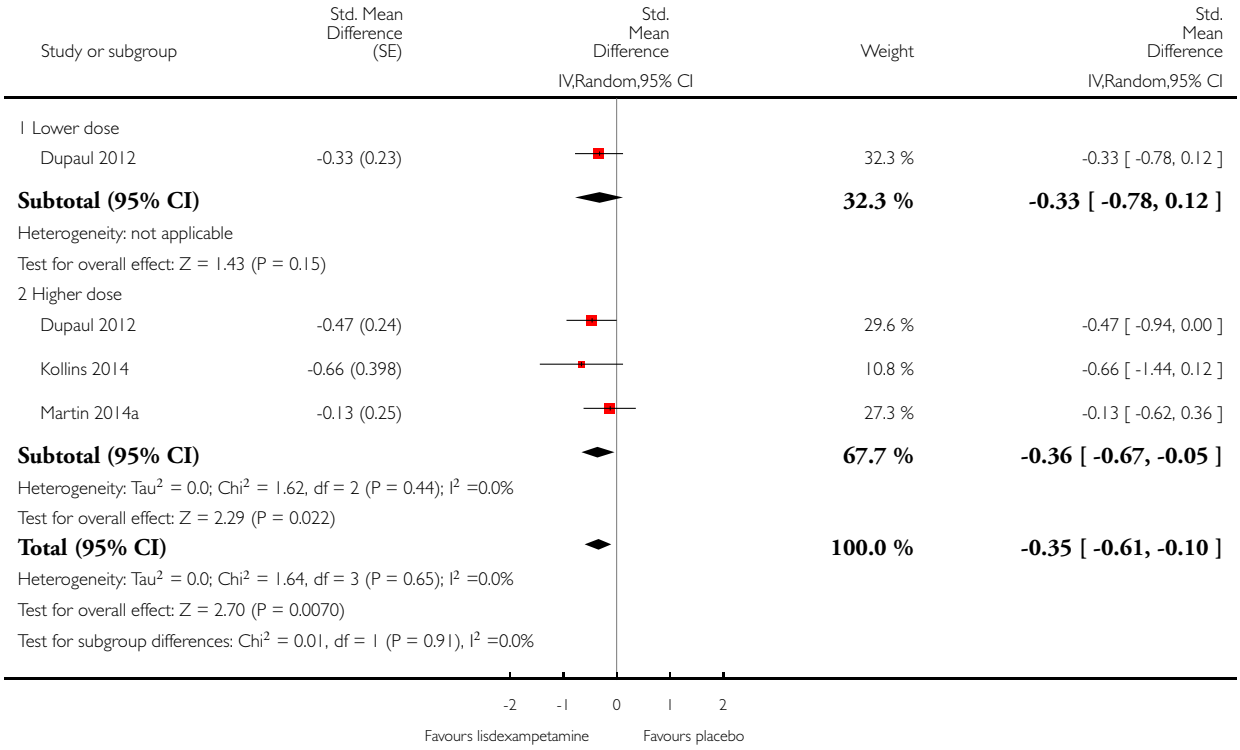
Analysis 5.2. Comparison 5 Subgroup analysis 3: dose of lisdexamfetamine, Outcome 2 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 5 Subgroup analysis 3: dose of lisdexamfetamine

Outcome: 2 ADHD symptom severity: patient rated



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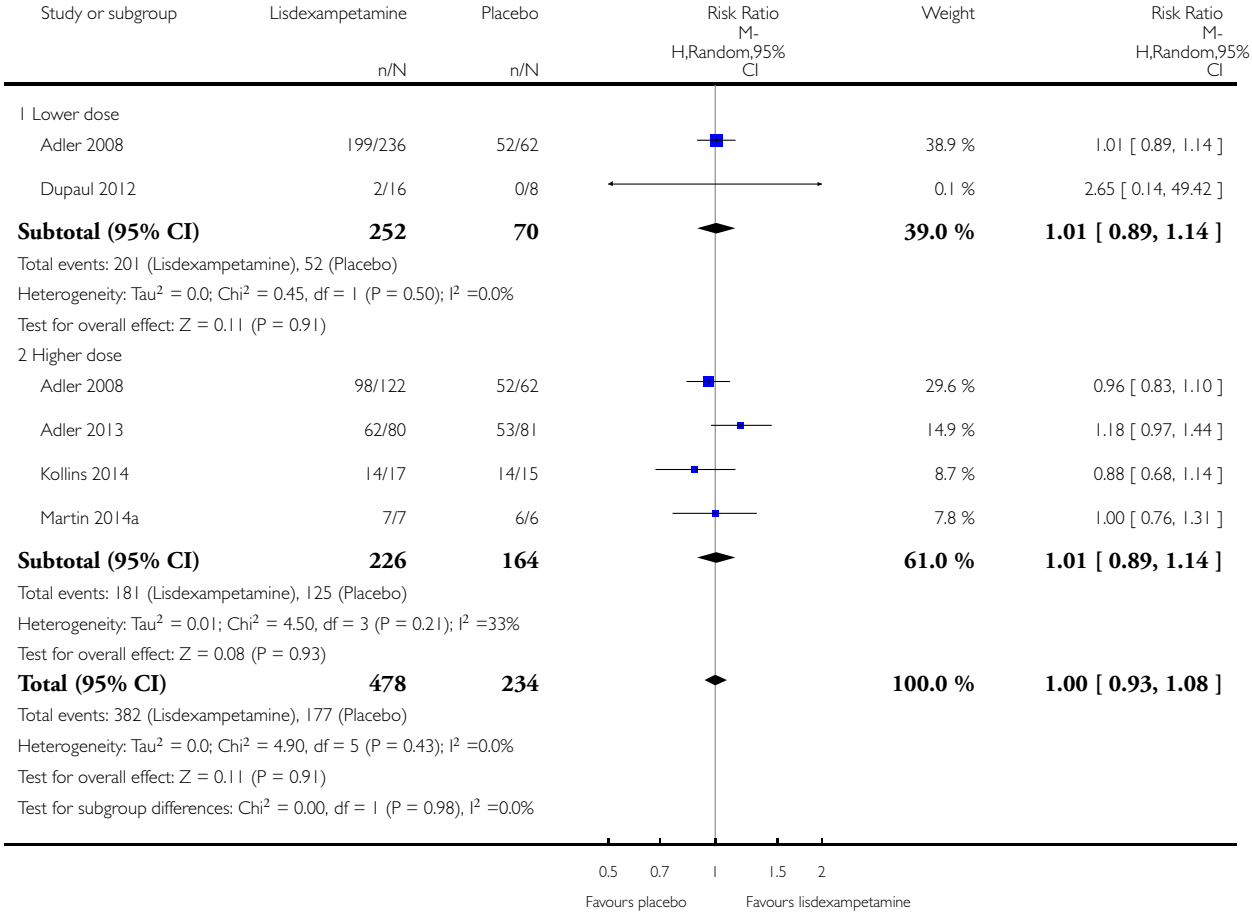
Analysis 5.3. Comparison 5 Subgroup analysis 3: dose of lisdexamfetamine, Outcome 3 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 5 Subgroup analysis 3: dose of lisdexamfetamine

Outcome: 3 Retention in treatment



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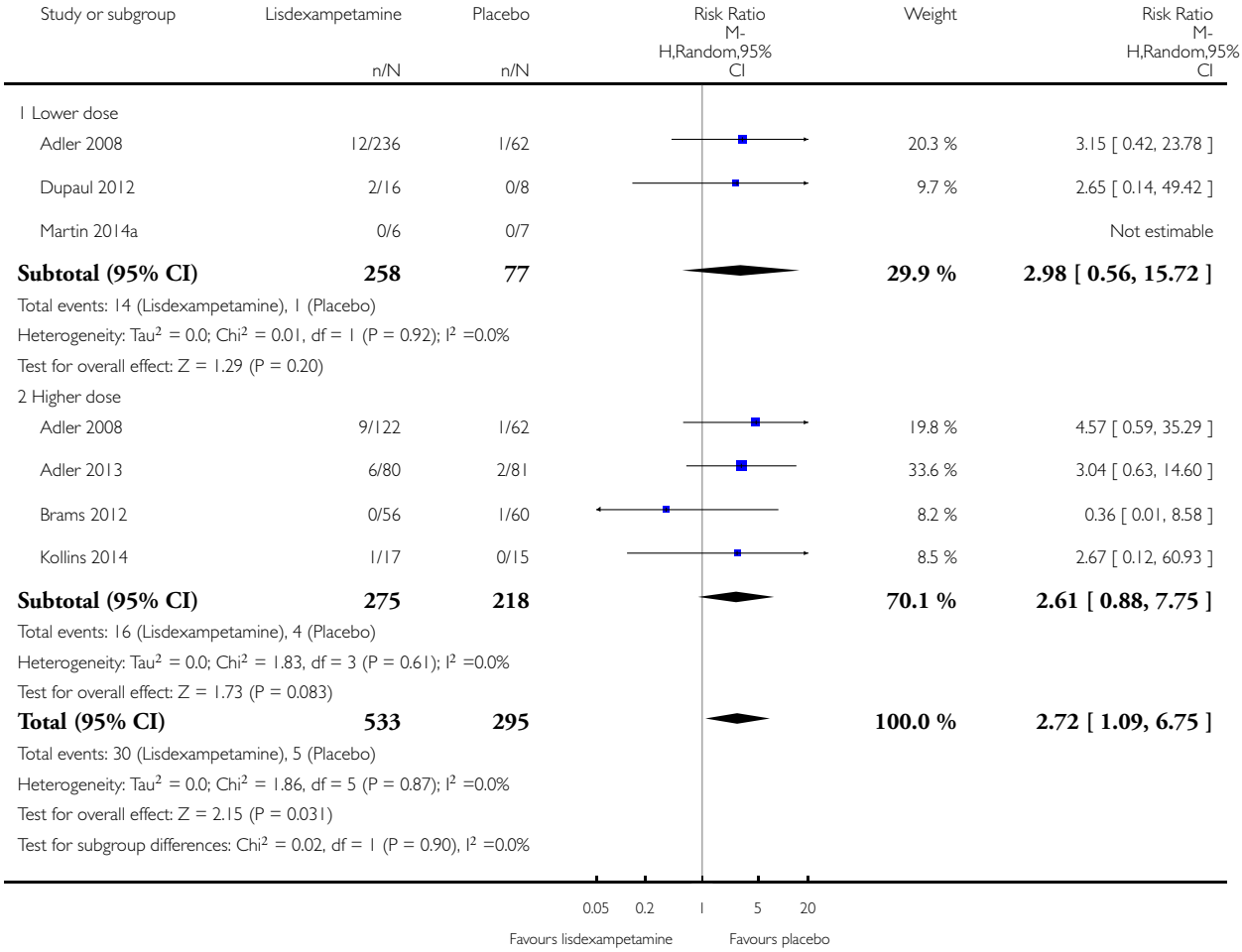
Analysis 5.4. Comparison 5 Subgroup analysis 3: dose of lisdexamfetamine, Outcome 4 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 5 Subgroup analysis 3: dose of lisdexamfetamine

Outcome: 4 Proportion of participants withdrawn owing to any adverse event



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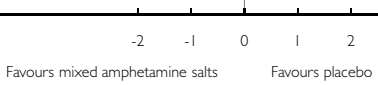
Analysis 6.1. Comparison 6 Subgroup analysis 3: dose of mixed amphetamine salts, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 6 Subgroup analysis 3: dose of mixed amphetamine salts

Outcome: 1 ADHD symptom severity: clinician rated

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Lower dose				
Frick 2017	-0.89 (0.148)		17.8 %	-0.89 [-1.18, -0.60]
Spencer 2008	-0.68 (0.13)		23.1 %	-0.68 [-0.93, -0.43]
Weisler 2017	-0.81 (0.1378)		20.6 %	-0.81 [-1.08, -0.54]
Subtotal (95% CI)			**61.5 %**	**-0.78 [-0.94, -0.63]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.19$, df = 2 (P = 0.55); $I^2 = 0.0\%$				
Test for overall effect: Z = 9.84 (P < 0.00001)				
2 Higher dose				
Frick 2017	-0.88 (0.1276)		24.0 %	-0.88 [-1.13, -0.63]
Levin 2015	-0.79 (0.199)		9.9 %	-0.79 [-1.18, -0.40]
Spencer 2001	-0.91 (0.29)		4.6 %	-0.91 [-1.48, -0.34]
Subtotal (95% CI)			**38.5 %**	**-0.86 [-1.06, -0.66]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 2 (P = 0.91); $I^2 = 0.0\%$				
Test for overall effect: Z = 8.54 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**-0.81 [-0.94, -0.69]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.72$, df = 5 (P = 0.89); $I^2 = 0.0\%$				
Test for overall effect: Z = 13.02 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 0.35$, df = 1 (P = 0.55), $I^2 = 0.0\%$				



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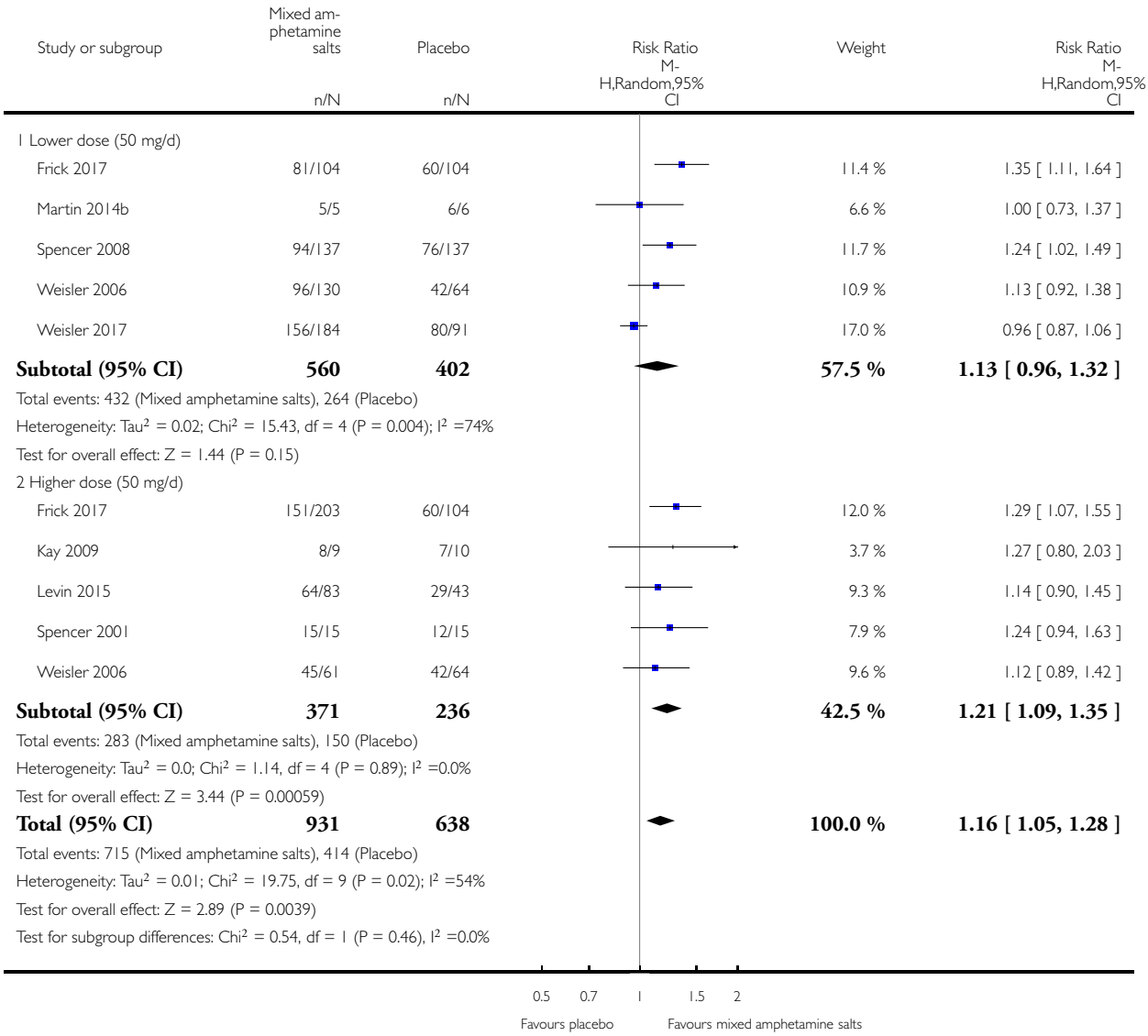
Analysis 6.2. Comparison 6 Subgroup analysis 3: dose of mixed amphetamine salts, Outcome 2 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 6 Subgroup analysis 3: dose of mixed amphetamine salts

Outcome: 2 Retention in treatment



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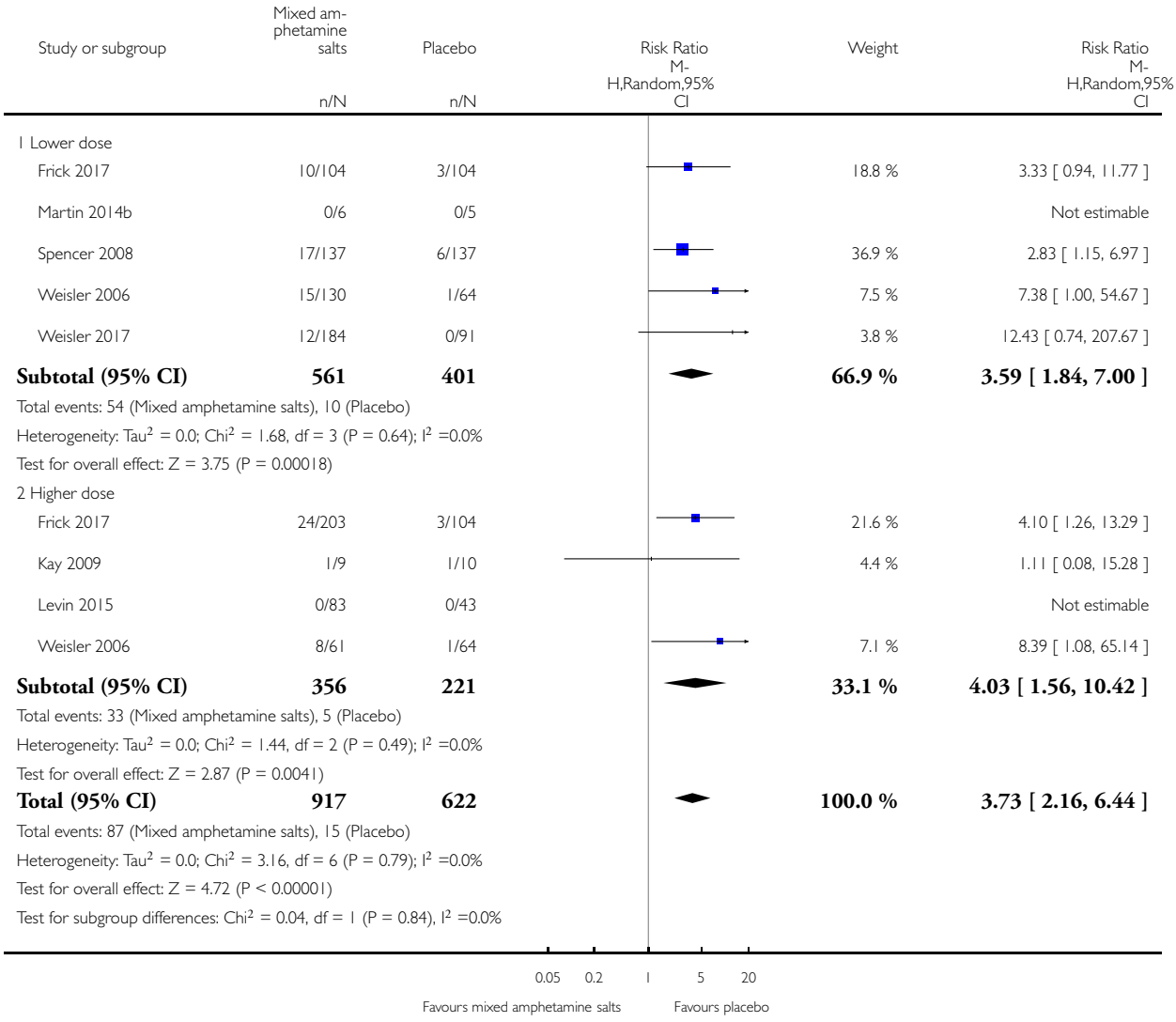
Analysis 6.3. Comparison 6 Subgroup analysis 3: dose of mixed amphetamine salts, Outcome 3 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 6 Subgroup analysis 3: dose of mixed amphetamine salts

Outcome: 3 Proportion of participants withdrawn owing to any adverse event



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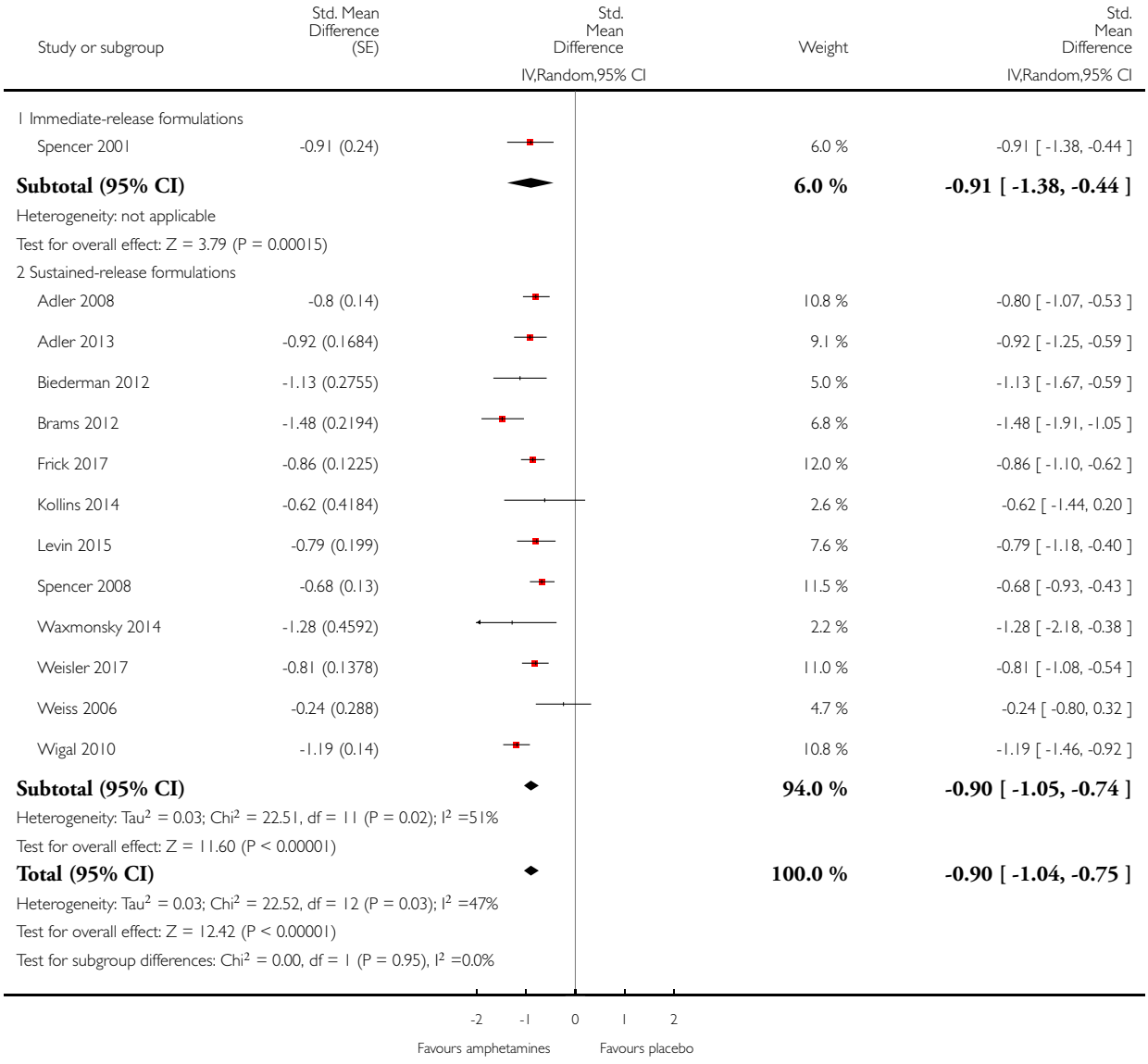
Analysis 7.1. Comparison 7 Subgroup analysis 4: type of drug-release formulation, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 7 Subgroup analysis 4: type of drug-release formulation

Outcome: 1 ADHD symptom severity: clinician rated



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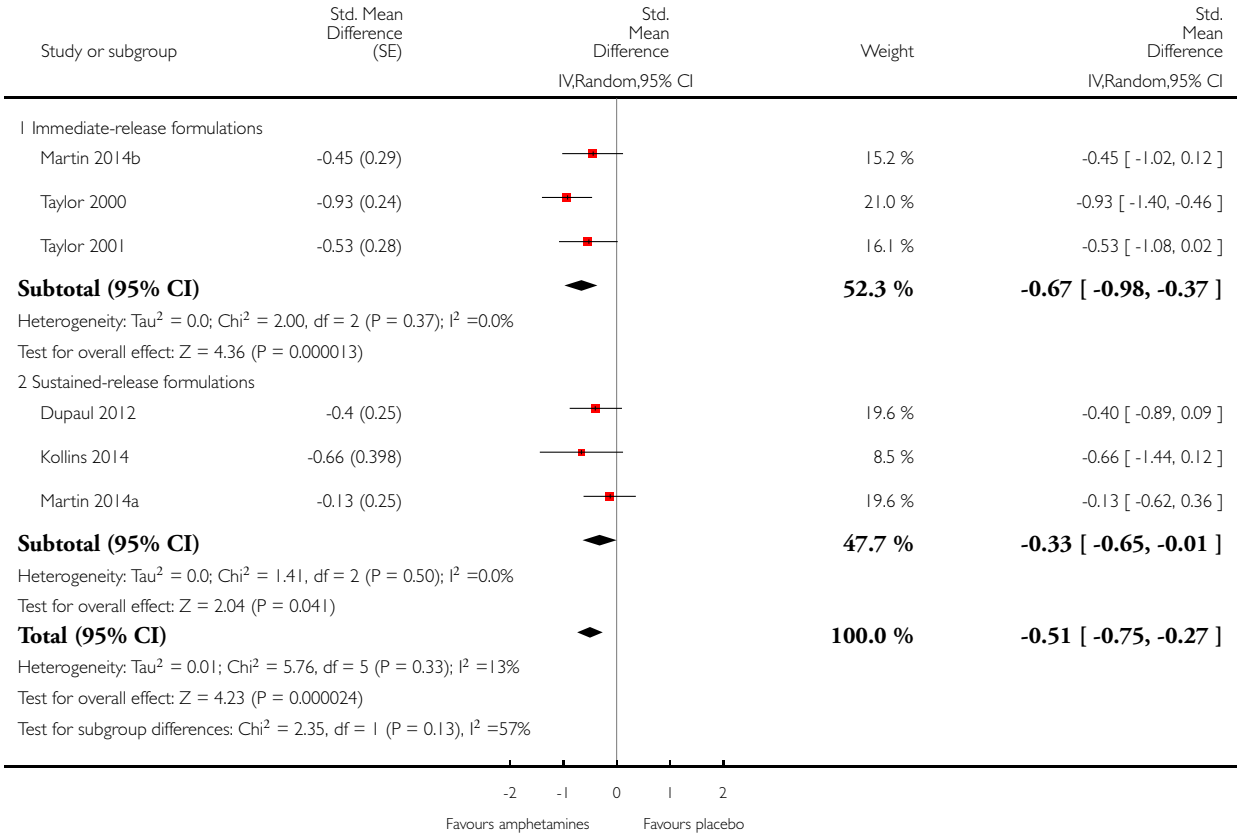
Analysis 7.2. Comparison 7 Subgroup analysis 4: type of drug-release formulation, Outcome 2 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 7 Subgroup analysis 4: type of drug-release formulation

Outcome: 2 ADHD symptom severity: patient rated



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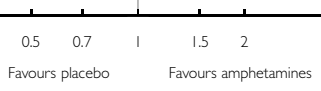
Analysis 7.3. Comparison 7 Subgroup analysis 4: type of drug-release formulation, Outcome 3 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 7 Subgroup analysis 4: type of drug-release formulation

Outcome: 3 Retention in treatment

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Immediate-release formulations					
Martin 2014b	5/5	6/6		3.5 %	1.00 [0.73, 1.37]
Spencer 2001	15/15	12/15		4.4 %	1.24 [0.94, 1.63]
Subtotal (95% CI)	**20**	**21**		**7.9 %**	**1.13 [0.91, 1.40]**
Total events: 20 (Amphetamines), 18 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.08$, df = 1 (P = 0.30); $I^2 = 7\%$					
Test for overall effect: Z = 1.11 (P = 0.27)					
2 Sustained-release formulations					
Adler 2008	297/358	52/62		11.0 %	0.99 [0.88, 1.11]
Adler 2013	62/80	53/81		6.8 %	1.18 [0.97, 1.44]
Biederman 2012	31/35	30/34		8.0 %	1.00 [0.85, 1.19]
Dupaul 2012	2/16	0/8		0.1 %	2.65 [0.14, 49.42]
Frick 2017	232/307	60/104		7.8 %	1.31 [1.10, 1.56]
Kay 2009	8/9	7/10		1.8 %	1.27 [0.80, 2.03]
Kollins 2014	14/17	14/15		4.8 %	0.88 [0.68, 1.14]
Levin 2015	64/83	29/43		5.4 %	1.14 [0.90, 1.45]
Martin 2014a	7/7	6/6		4.4 %	1.00 [0.76, 1.31]
Spencer 2008	94/137	76/137		7.2 %	1.24 [1.02, 1.49]
Waxmonsky 2014	11/13	13/14		4.4 %	0.91 [0.69, 1.20]
Weisler 2006	141/191	42/64		6.9 %	1.12 [0.92, 1.37]
Weisler 2017	156/184	80/91		12.4 %	0.96 [0.87, 1.06]
Weiss 2006	14/23	20/26		2.5 %	0.79 [0.54, 1.17]
Wigal 2010	53/63	52/64		8.6 %	1.04 [0.88, 1.21]
Subtotal (95% CI)	**1523**	**759**		**92.1 %**	**1.06 [0.98, 1.13]**
Total events: 1186 (Amphetamines), 534 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.31$, df = 14 (P = 0.03); $I^2 = 45\%$					
Test for overall effect: Z = 1.48 (P = 0.14)					



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Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**1543**	**780**		**100.0 %**	**1.06 [0.99, 1.13]**
Total events: 1206 (Amphetamines), 552 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 26.69, df = 16 (P = 0.05); I^2 =40%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi^2 = 0.34, df = 1 (P = 0.56), I^2 =0.0%					

Analysis 8.1. Comparison 8 Sensitivity analysis: incomplete subjective outcome data, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 8 Sensitivity analysis: incomplete subjective outcome data

Outcome: 1 ADHD symptom severity: clinician rated

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Adler 2008	-0.8 (0.14)		-0.80 [-1.07, -0.53]

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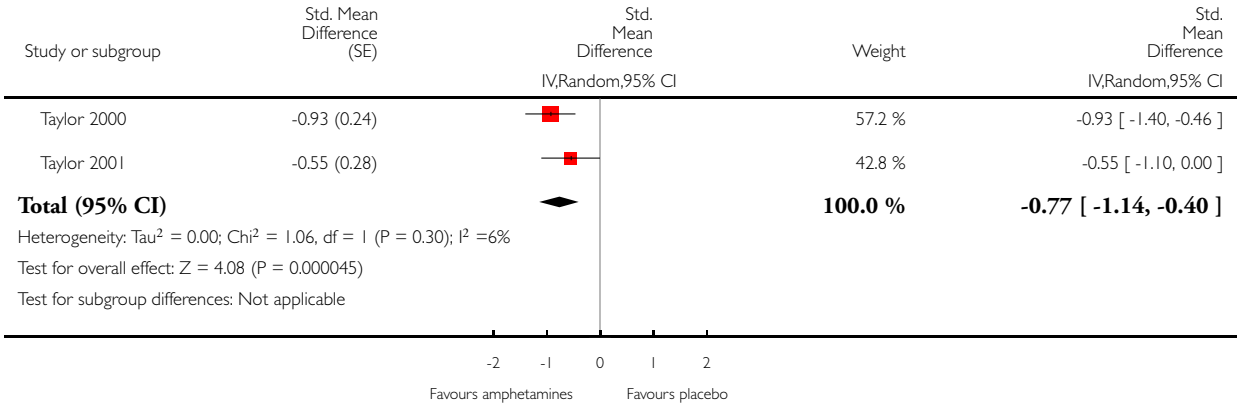
Analysis 8.2. Comparison 8 Sensitivity analysis: incomplete subjective outcome data, Outcome 2 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 8 Sensitivity analysis: incomplete subjective outcome data

Outcome: 2 ADHD symptom severity: patient rated



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Analysis 9.1. Comparison 9 Sensitivity analysis: other potential sources of bias, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 9 Sensitivity analysis: other potential sources of bias

Outcome: 1 ADHD symptom severity: clinician rated

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Adler 2008	-0.8 (0.14)		15.3 %	-0.80 [-1.07, -0.53]
Adler 2013	-0.92 (0.1684)		13.2 %	-0.92 [-1.25, -0.59]
Biederman 2012	-1.13 (0.2755)		7.5 %	-1.13 [-1.67, -0.59]
Brams 2012	-1.48 (0.2194)		10.1 %	-1.48 [-1.91, -1.05]
Kollins 2014	-0.62 (0.4184)		4.0 %	-0.62 [-1.44, 0.20]
Levin 2015	-0.79 (0.199)		11.2 %	-0.79 [-1.18, -0.40]
Spencer 2008	-0.68 (0.13)		16.1 %	-0.68 [-0.93, -0.43]
Weisler 2017	-0.81 (0.1378)		15.5 %	-0.81 [-1.08, -0.54]
Weiss 2006	-0.24 (0.288)		7.1 %	-0.24 [-0.80, 0.32]
Total (95% CI)			**100.0 %**	**-0.84 [-1.02, -0.66]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 16.14$, df = 8 (P = 0.04); $I^2 = 50\%$

Test for overall effect: Z = 9.23 (P < 0.00001)

Test for subgroup differences: Not applicable

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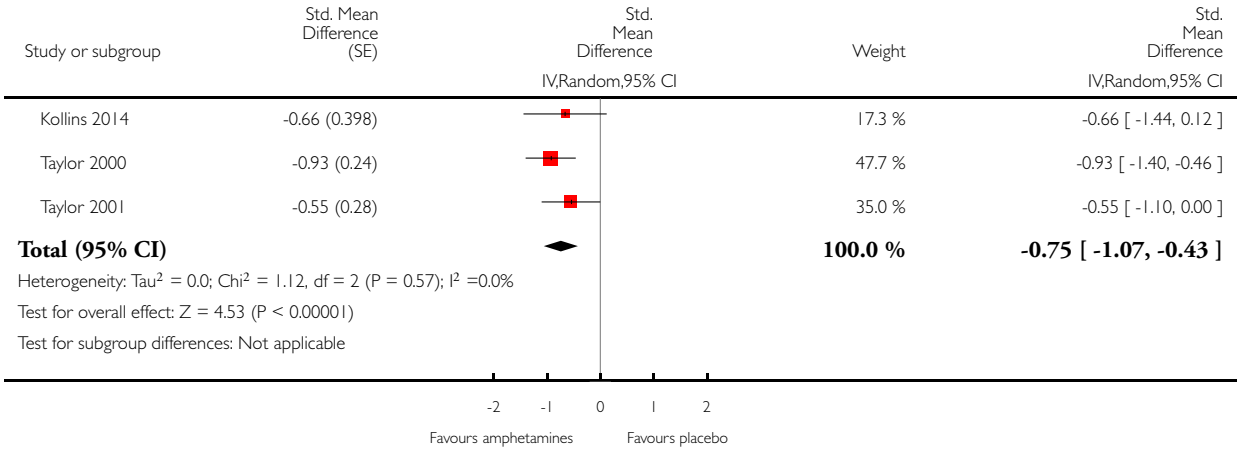
Analysis 9.2. Comparison 9 Sensitivity analysis: other potential sources of bias, Outcome 2 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 9 Sensitivity analysis: other potential sources of bias

Outcome: 2 ADHD symptom severity: patient rated



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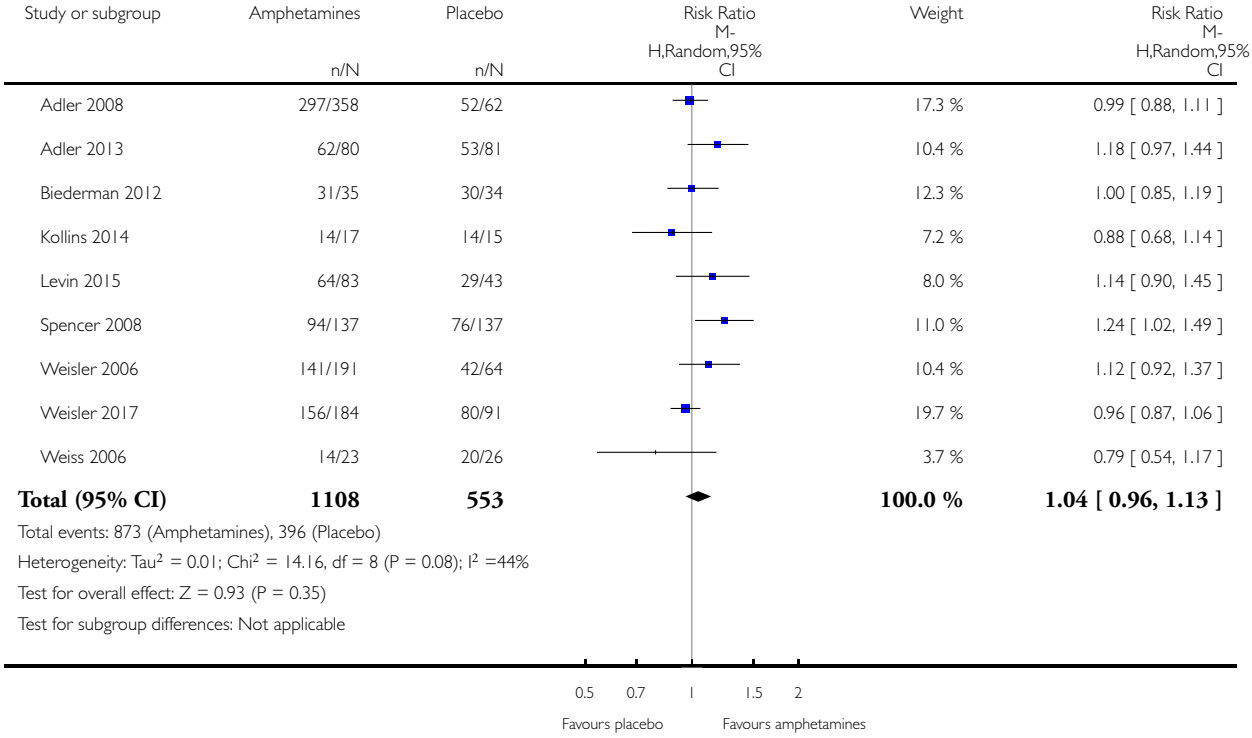
Analysis 9.3. Comparison 9 Sensitivity analysis: other potential sources of bias, Outcome 3 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 9 Sensitivity analysis: other potential sources of bias

Outcome: 3 Retention in treatment



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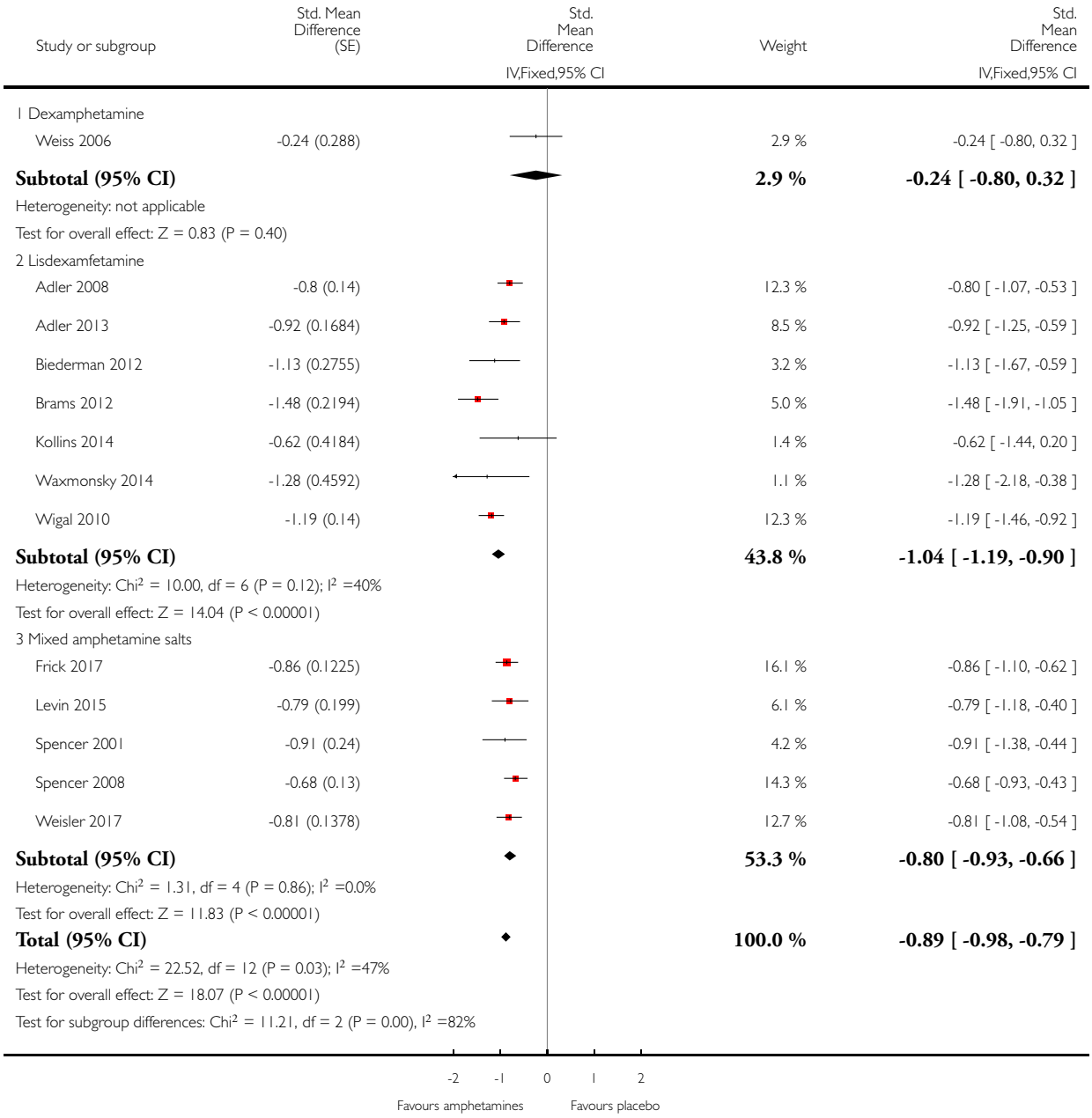
Analysis 10.1. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 1 ADHD symptom severity: clinician-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 1 ADHD symptom severity: clinician-rated



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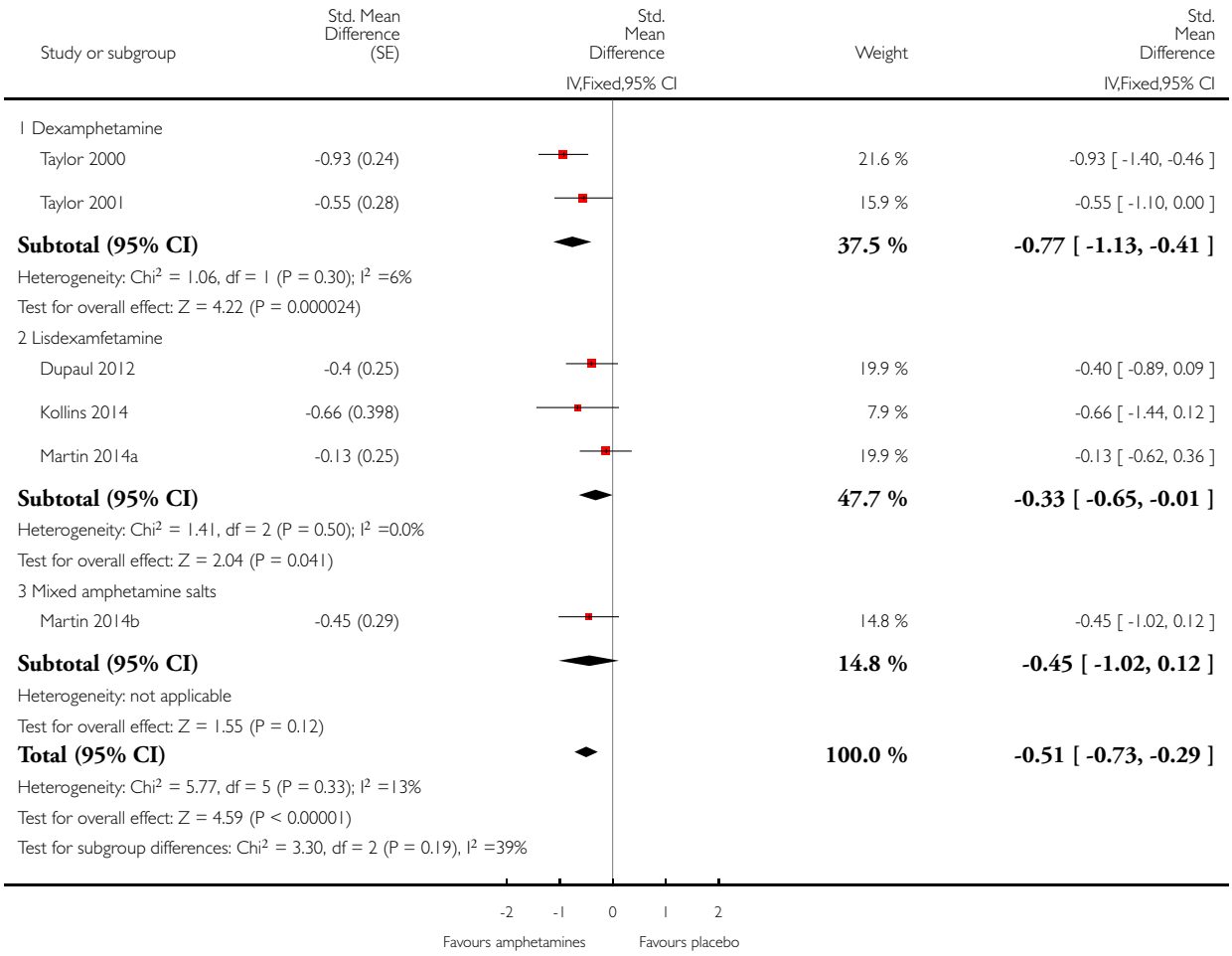
Analysis 10.2. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 2 ADHD symptom severity: patient-rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 2 ADHD symptom severity: patient-rated



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Analysis 10.3. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 3 Clinical impression of severity at study end.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 3 Clinical impression of severity at study end

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Spencer 2001	27	3.4 (1)	27	4.4 (0.9)		70.7 %	-1.04 [-1.61, -0.47]
Waxmonsky 2014	11	1.36 (0.81)	13	2.38 (0.81)		29.3 %	-1.22 [-2.10, -0.33]
Total (95% CI)	**38**		**40**			**100.0 %**	**-1.09 [-1.57, -0.61]**

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 10.4. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 4 Clinical impression of improvement at study end.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 4 Clinical impression of improvement at study end

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Weisler 2017	177	2.2 (1.27)	86	3.1 (1.05)		100.0 %	-0.75 [-1.01, -0.48]
Total (95% CI)	**177**		**86**			**100.0 %**	**-0.75 [-1.01, -0.48]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.51 (P < 0.00001)

Test for subgroup differences: Not applicable

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Analysis 10.5. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 5 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms

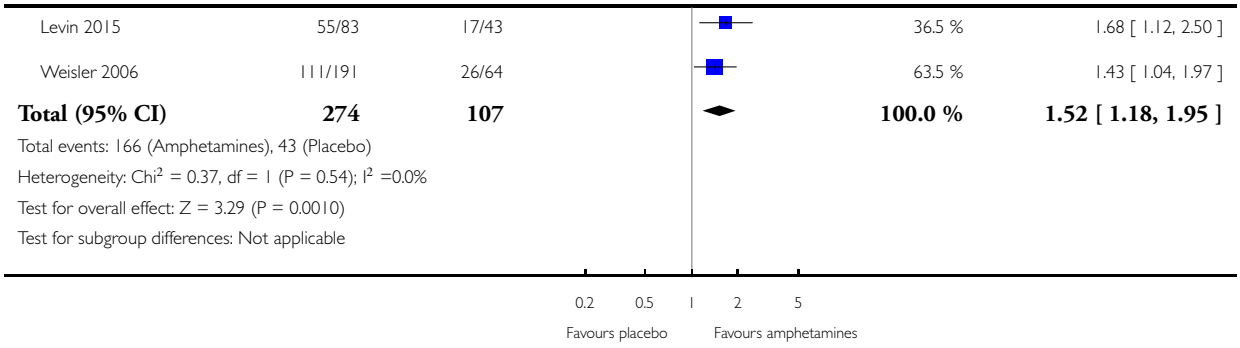
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Levin 2015	55/83	17/43		36.5 %	1.68 [1.12, 2.50]
Weisler 2006	111/191	26/64		63.5 %	1.43 [1.04, 1.97]
Total (95% CI)	**274**	**107**		**100.0 %**	**1.52 [1.18, 1.95]**

Total events: 166 (Amphetamines), 43 (Placebo)

Heterogeneity: $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 3.29 (P = 0.0010)

Test for subgroup differences: Not applicable



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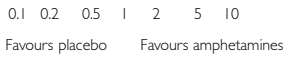
Analysis 10.6. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 6 Proportion of participants achieving a CGI-Improvement score of 1 or 2.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 6 Proportion of participants achieving a CGI-Improvement score of 1 or 2

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adler 2008	206/358	18/62		19.8 %	1.98 [1.33, 2.95]
Adler 2013	62/79	26/75		17.2 %	2.26 [1.63, 3.15]
Frick 2017	197/302	21/103		20.3 %	3.20 [2.17, 4.73]
Levin 2015	31/83	5/43		4.3 %	3.21 [1.35, 7.67]
Spencer 2008	70/137	28/137		18.1 %	2.50 [1.73, 3.61]
Waxmonsky 2014	9/11	4/13		2.4 %	2.66 [1.12, 6.29]
Weisler 2006	103/191	16/64		15.5 %	2.16 [1.38, 3.36]
Weiss 2006	15/23	4/26		2.4 %	4.24 [1.64, 10.96]
Total (95% CI)	**1184**	**523**		**100.0 %**	**2.52 [2.14, 2.97]**
Total events: 693 (Amphetamines), 122 (Placebo)					
Heterogeneity: Chi^2 = 5.17, df = 7 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 10.96 (P < 0.00001)					
Test for subgroup differences: Not applicable					



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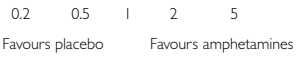
Analysis 10.7. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 7 Proportion of participants achieving a reduction ≥ 30% in severity of ADHD symptoms and a CGI-Improvement score of 1 or 2

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biederman 2012	21/31	8/30		100.0 %	2.54 [1.34, 4.82]
Total (95% CI)	**31**	**30**		**100.0 %**	**2.54 [1.34, 4.82]**
Total events: 21 (Amphetamines), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.85 (P = 0.0044)					
Test for subgroup differences: Not applicable					



Analysis 10.8. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 8 Global functioning.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 8 Global functioning

Study or subgroup	Amphetamines N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Biederman 2012	31	63.5 (4.4)	30	58.9 (4.8)		52.5 %	0.99 [0.45, 1.52]
Weiss 2006	23	60 (15.89)	26	58.88 (9.84)		47.5 %	0.08 [-0.48, 0.65]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.56 [0.17, 0.95]**
Heterogeneity: Chi^2 = 5.22, df = 1 (P = 0.02); I^2 =81%							
Test for overall effect: Z = 2.83 (P = 0.0046)							
Test for subgroup differences: Not applicable							

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Analysis 10.9. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 9 Depressive symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 9 Depressive symptoms

Study or subgroup	Amphetamines		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Biederman 2012	31	1.3 (1.7)	30	1.2 (1.6)		55.8 %	0.06 [-0.44, 0.56]
Weiss 2006	23	7.56 (7.25)	26	6 (3.29)		44.2 %	0.28 [-0.29, 0.84]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.16 [-0.22, 0.53]**

Heterogeneity: $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

Analysis 10.10. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 10 Anxiety symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 10 Anxiety symptoms

Study or subgroup	Amphetamines		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Biederman 2012	31	1.5 (1.9)	30	1.4 (2.1)		55.7 %	0.05 [-0.45, 0.55]
Weiss 2006	23	9.17 (7.8)	26	7.69 (4.47)		44.3 %	0.23 [-0.33, 0.80]
Total (95% CI)	**54**		**56**			**100.0 %**	**0.13 [-0.24, 0.51]**

Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 0.68 (P = 0.49)

Test for subgroup differences: Not applicable

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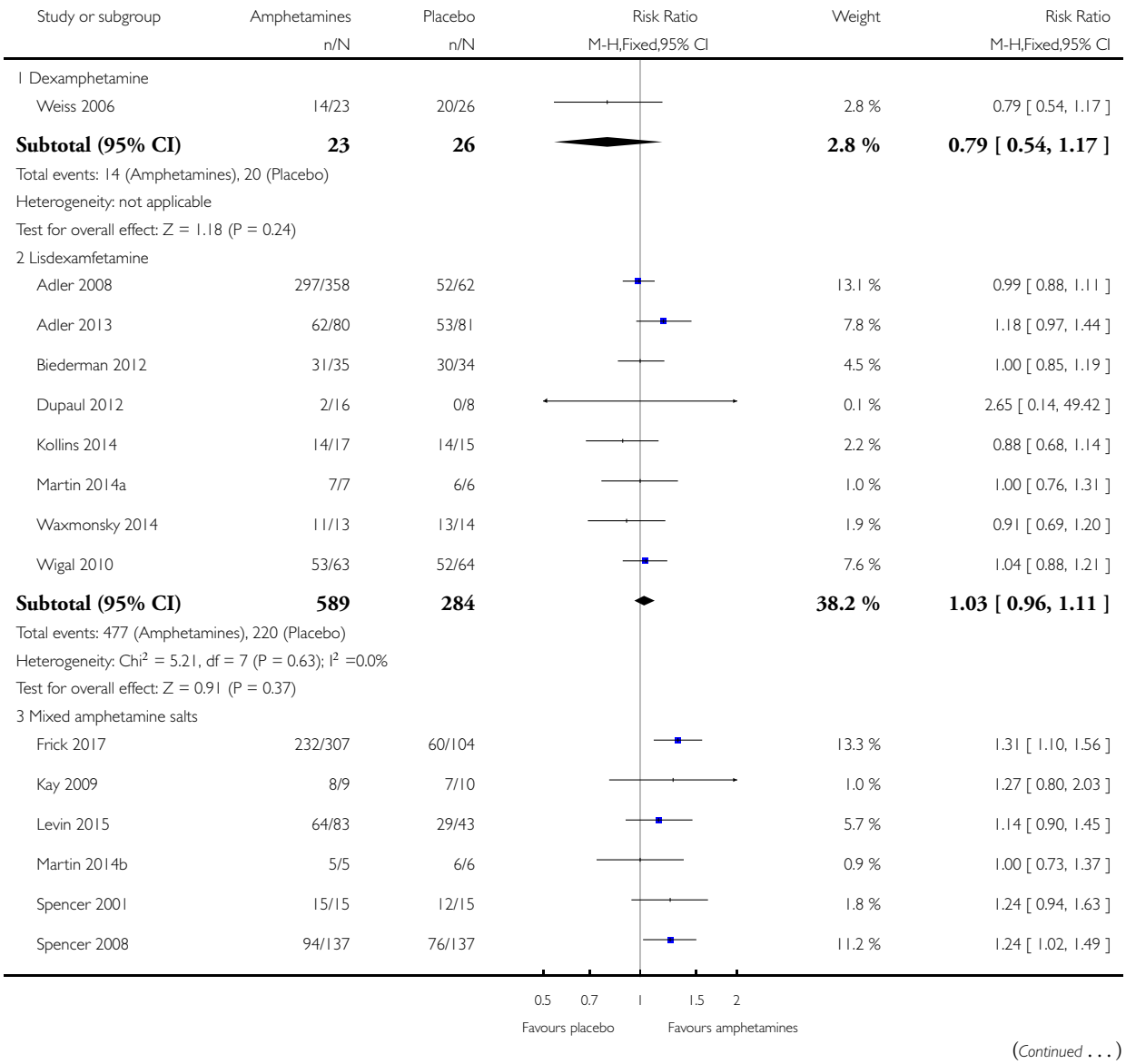
Analysis 10.11. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 11 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 11 Retention in treatment



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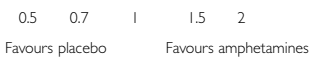
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Weisler 2006	141/191	42/64		9.3 %	1.12 [0.92, 1.37]
Weisler 2017	156/184	80/91		15.8 %	0.96 [0.87, 1.06]
Subtotal (95% CI)	**931**	**470**		**59.0 %**	**1.15 [1.07, 1.24]**
Total events: 715 (Amphetamines), 312 (Placebo)					
Heterogeneity: Chi^2 = 16.44, df = 7 (P = 0.02); I^2 =57%					
Test for overall effect: Z = 3.75 (P = 0.00017)					
Total (95% CI)	**1543**	**780**		**100.0 %**	**1.10 [1.04, 1.16]**
Total events: 1206 (Amphetamines), 552 (Placebo)					
Heterogeneity: Chi^2 = 26.69, df = 16 (P = 0.05); I^2 =40%					
Test for overall effect: Z = 3.41 (P = 0.00065)					
Test for subgroup differences: Chi^2 = 6.61, df = 2 (P = 0.04), I^2 =70%					



Analysis 10.12. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 12 Proportion of participants withdrawn owing to any cardiovascular adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 12 Proportion of participants withdrawn owing to any cardiovascular adverse event

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adler 2008	7/358	0/62		53.2 %	2.63 [0.15, 45.51]
Weisler 2006	3/191	0/64		46.8 %	2.37 [0.12, 45.27]
Total (95% CI)	**549**	**126**		**100.0 %**	**2.51 [0.32, 19.54]**
Total events: 10 (Amphetamines), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 0.88 (P = 0.38)					
Test for subgroup differences: Not applicable					

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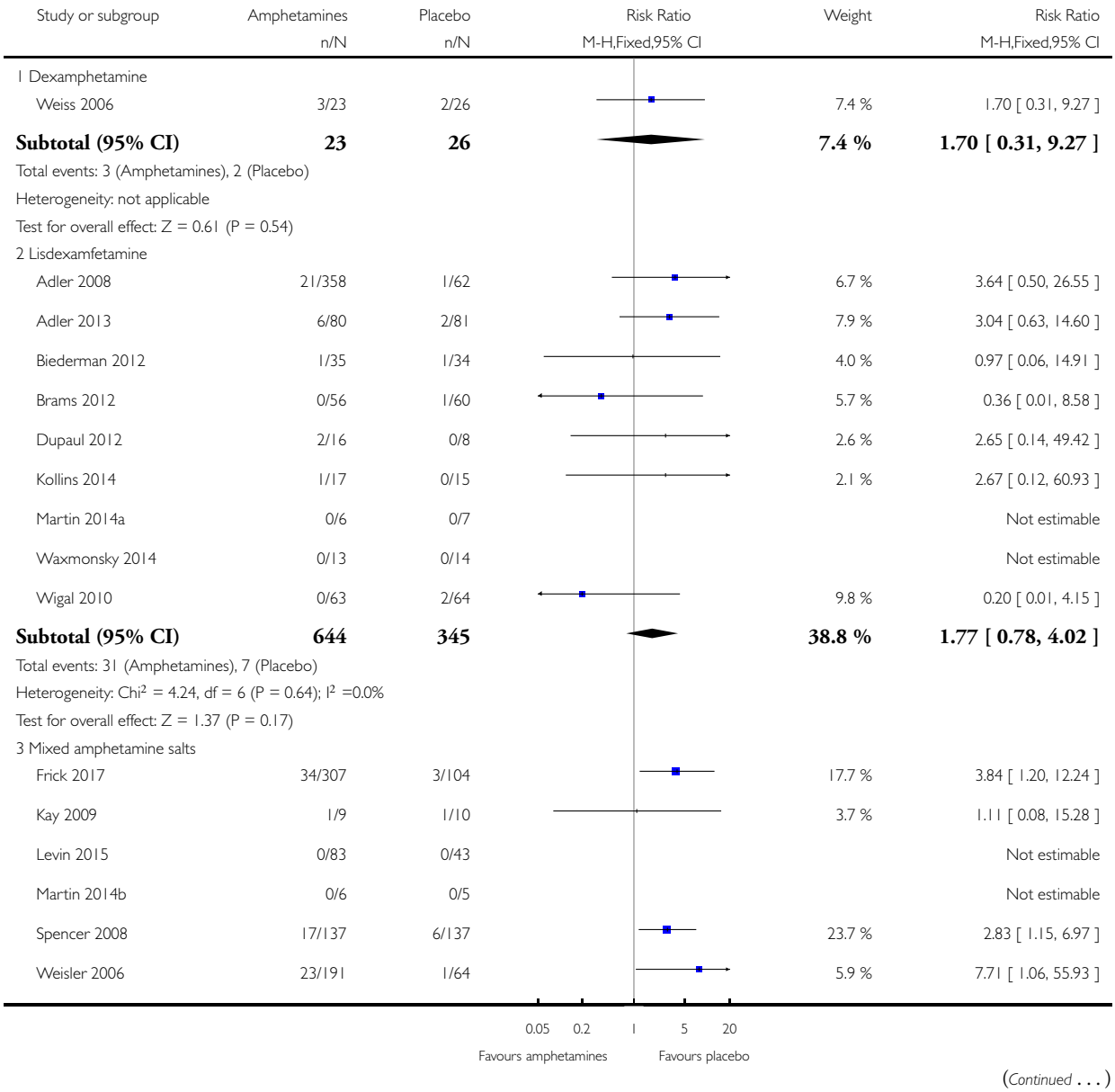
Analysis 10.13. Comparison 10 Sensitivity analysis: fixed-effect model, Outcome 13 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 10 Sensitivity analysis: fixed-effect model

Outcome: 13 Proportion of participants withdrawn owing to any adverse event



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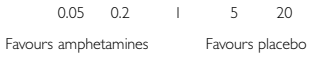
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Weisler 2017	12/184	0/91		2.6 %	12.43 [0.74, 207.67]
Subtotal (95% CI)	**917**	**454**		**53.8 %**	**4.05 [2.14, 7.67]**
Total events: 87 (Amphetamines), 11 (Placebo)					
Heterogeneity: Chi^2 = 2.57, df = 4 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
Total (95% CI)	**1584**	**825**		**100.0 %**	**2.99 [1.86, 4.83]**
Total events: 121 (Amphetamines), 20 (Placebo)					
Heterogeneity: Chi^2 = 8.50, df = 12 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 4.50 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.82, df = 2 (P = 0.24), I^2 =29%					



Analysis 11.1. Comparison 11 Post hoc sensitivity analysis 1: calculation of effect sizes using correlation coefficient from Taylor 2000, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 11 Post hoc sensitivity analysis 1: calculation of effect sizes using correlation coefficient from Taylor 2000

Outcome: 1 ADHD symptom severity: clinician rated

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Adler 2008	-0.8 (0.14)		10.2 %	-0.80 [-1.07, -0.53]
Adler 2013	-0.92 (0.1684)		8.8 %	-0.92 [-1.25, -0.59]
Biederman 2012	-1.13 (0.2755)		5.0 %	-1.13 [-1.67, -0.59]
Brams 2012	-1.48 (0.2194)		6.7 %	-1.48 [-1.91, -1.05]
Frick 2017	-0.86 (0.1225)		11.2 %	-0.86 [-1.10, -0.62]
Kollins 2014	-0.62 (0.4184)		2.7 %	-0.62 [-1.44, 0.20]
Levin 2015	-0.79 (0.199)		7.5 %	-0.79 [-1.18, -0.40]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Spencer 2001	-0.91 (0.2)		7.4 %	-0.91 [-1.30, -0.52]
Spencer 2008	-0.68 (0.13)		10.8 %	-0.68 [-0.93, -0.43]
Waxmonsky 2014	-1.28 (0.4592)		2.3 %	-1.28 [-2.18, -0.38]
Weisler 2017	-0.81 (0.1378)		10.3 %	-0.81 [-1.08, -0.54]
Weiss 2006	-0.24 (0.288)		4.7 %	-0.24 [-0.80, 0.32]
Wigal 2010	-1.19 (0.1)		12.4 %	-1.19 [-1.39, -0.99]
Total (95% CI)			**100.0 %**	**-0.90 [-1.05, -0.76]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 26.54$, df = 12 (P = 0.01); $I^2 = 55\%$

Test for overall effect: Z = 12.09 (P < 0.00001)

Test for subgroup differences: Not applicable

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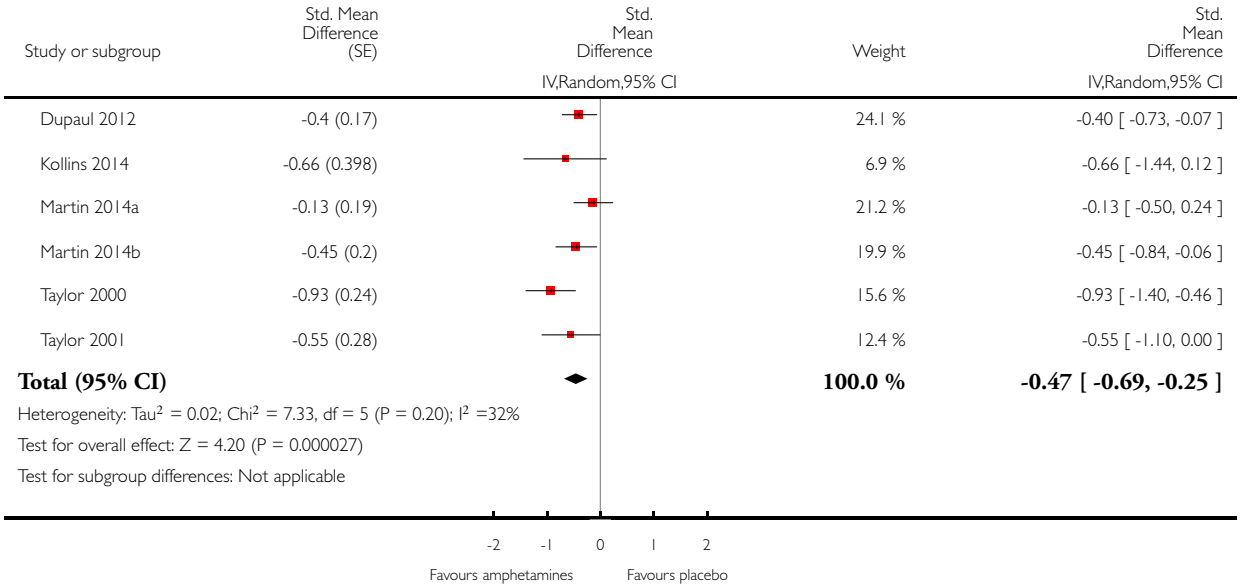
Analysis 11.2. Comparison 11 Post hoc sensitivity analysis 1: calculation of effect sizes using correlation coefficient from Taylor 2000, Outcome 2 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 11 Post hoc sensitivity analysis 1: calculation of effect sizes using correlation coefficient from Taylor 2000

Outcome: 2 ADHD symptom severity: patient rated



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Analysis 12.1. Comparison 12 Post hoc sensitivity analysis 2: pooled risk difference for proportion of participants withdrawn owing to cardiovascular adverse events and any adverse event, Outcome 1 Proportion of participants withdrawn owing to any cardiovascular adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 12 Post hoc sensitivity analysis 2: pooled risk difference for proportion of participants withdrawn owing to cardiovascular adverse events and any adverse event

Outcome: 1 Proportion of participants withdrawn owing to any cardiovascular adverse event

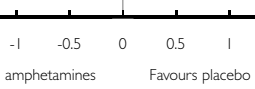
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Adler 2008	7/358	0/62		53.2 %	0.02 [-0.01, 0.05]
Dupaul 2012	1/16	0/8		0.9 %	0.06 [-0.14, 0.26]
Weisler 2006	3/191	0/64		45.9 %	0.02 [-0.01, 0.04]
Total (95% CI)	**565**	**134**		**100.0 %**	**0.02 [0.00, 0.04]**

Total events: 11 (Amphetamines), 0 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 1.85 (P = 0.065)

Test for subgroup differences: Not applicable



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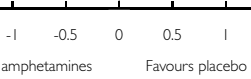
Analysis 12.2. Comparison 12 Post hoc sensitivity analysis 2: pooled risk difference for proportion of participants withdrawn owing to cardiovascular adverse events and any adverse event, Outcome 2 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 12 Post hoc sensitivity analysis 2: pooled risk difference for proportion of participants withdrawn owing to cardiovascular adverse events and any adverse event

Outcome: 2 Proportion of participants withdrawn owing to any adverse event

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Dexamphetamine					
Weiss 2006	3/23	2/26		2.0 %	0.05 [-0.12, 0.23]
Subtotal (95% CI)	**23**	**26**		**2.0 %**	**0.05 [-0.12, 0.23]**
Total events: 3 (Amphetamines), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Lisdexamfetamine					
Adler 2008	21/358	1/62		10.4 %	0.04 [0.00, 0.08]
Adler 2013	6/80	2/81		7.2 %	0.05 [-0.02, 0.12]
Biederman 2012	1/35	1/34		6.1 %	0.00 [-0.08, 0.08]
Brams 2012	0/56	1/60		9.6 %	-0.02 [-0.06, 0.03]
Dupaul 2012	2/16	0/8		1.2 %	0.13 [-0.10, 0.35]
Kollins 2014	1/17	0/15		2.4 %	0.06 [-0.09, 0.21]
Martin 2014a	0/6	0/7		1.0 %	0.0 [-0.25, 0.25]
Waxmonsky 2014	0/13	0/14		3.0 %	0.0 [-0.13, 0.13]
Wigal 2010	0/63	2/64		8.9 %	-0.03 [-0.08, 0.02]
Subtotal (95% CI)	**644**	**345**		**49.8 %**	**0.01 [-0.02, 0.04]**
Total events: 31 (Amphetamines), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.77$, df = 8 (P = 0.28); $I^2 = 18\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
3 Mixed amphetamine salts					
Frick 2017	34/307	3/104		9.4 %	0.08 [0.03, 0.13]
Kay 2009	1/9	1/10		0.8 %	0.01 [-0.27, 0.29]
Levin 2015	0/83	0/43		10.9 %	0.0 [-0.04, 0.04]
Martin 2014b	0/6	0/5		0.8 %	0.0 [-0.29, 0.29]
Spencer 2008	17/137	6/137		7.4 %	0.08 [0.02, 0.15]



(*Continued* . . .)

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(. . . *Continued*)

Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Weisler 2006	23/191	1/64		8.5 %	0.10 [0.05, 0.16]
Weisler 2017	12/184	0/91		10.5 %	0.07 [0.03, 0.10]
Subtotal (95% CI)	**917**	**454**		**48.2 %**	**0.06 [0.02, 0.10]**
Total events: 87 (Amphetamines), 11 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 17.99$, df = 6 (P = 0.01); $I^2 = 67\%$					
Test for overall effect: Z = 2.95 (P = 0.0032)					
Total (95% CI)	**1584**	**825**		**100.0 %**	**0.04 [0.01, 0.06]**
Total events: 121 (Amphetamines), 20 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 36.02$, df = 16 (P = 0.003); $I^2 = 56\%$					
Test for overall effect: Z = 2.78 (P = 0.0054)					
Test for subgroup differences: $Chi^2 = 4.09$, df = 2 (P = 0.13), $I^2 = 51\%$					

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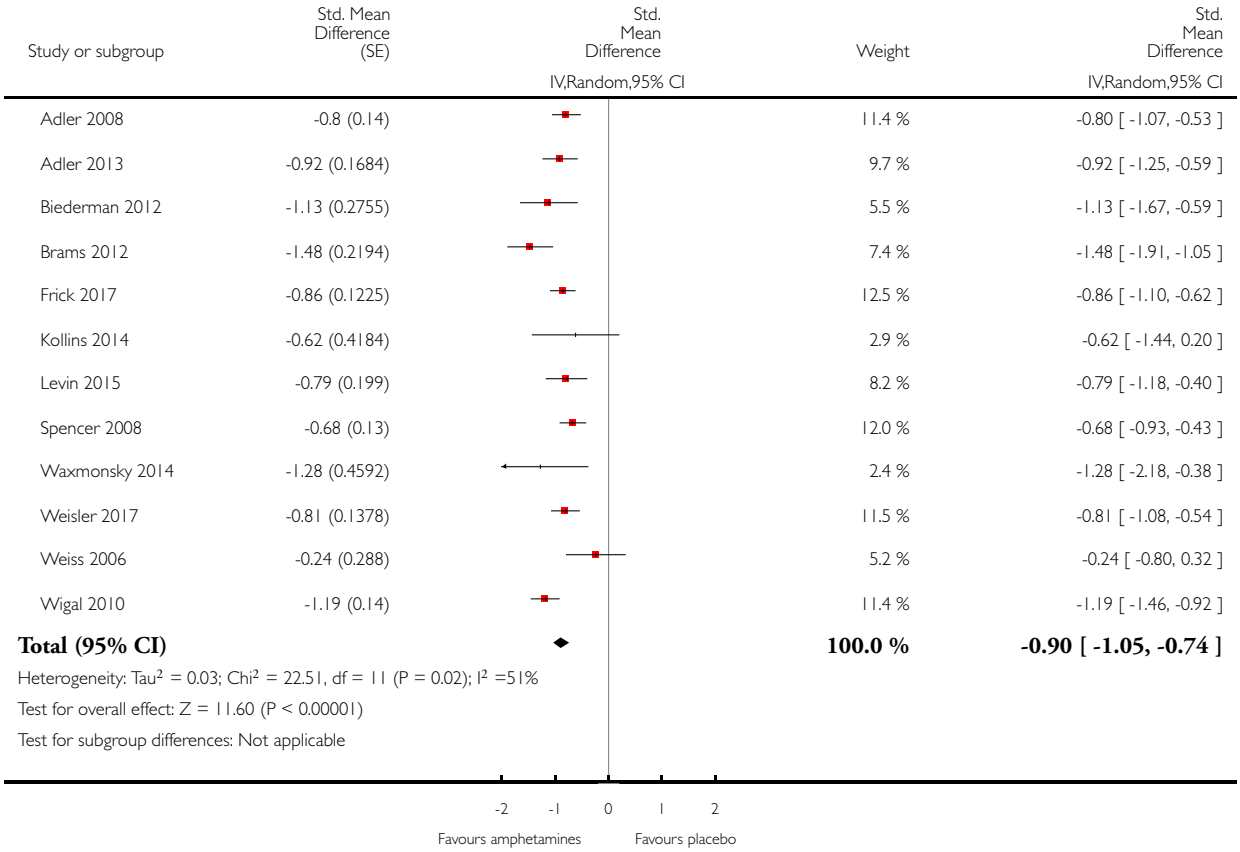
Analysis 13.1. Comparison 13 Post hoc sensitivity analysis 3: exclusion of cross-over study, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 13 Post hoc sensitivity analysis 3: exclusion of cross-over study

Outcome: 1 ADHD symptom severity: clinician rated



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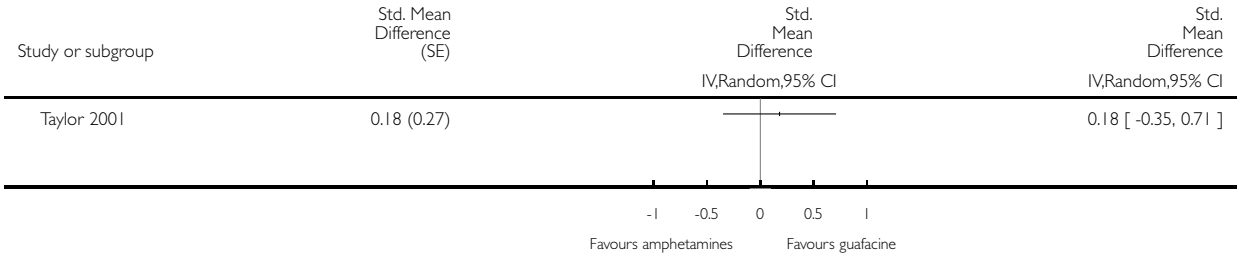
Analysis 14.1. Comparison 14 Amphetamines vs guanfacine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 1 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 14 Amphetamines vs guanfacine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 1 ADHD symptom severity: patient rated

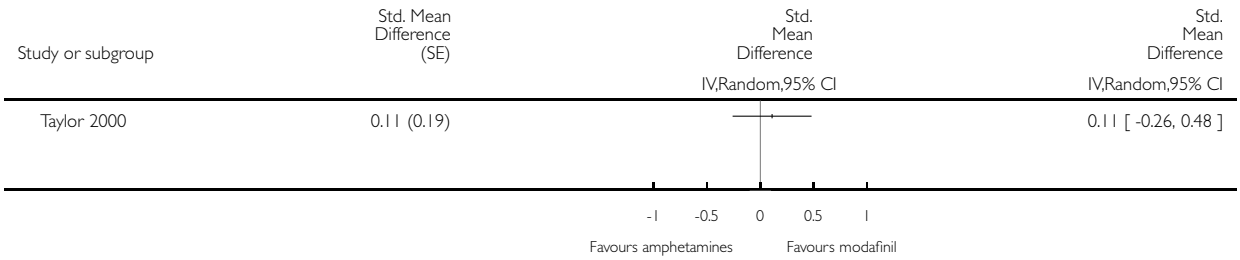


Analysis 15.1. Comparison 15 Amphetamines vs modafinil for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 1 ADHD symptom severity: patient rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 15 Amphetamines vs modafinil for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 1 ADHD symptom severity: patient rated



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Analysis 16.1. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 1 ADHD symptom severity: clinician rated.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 1 ADHD symptom severity: clinician rated

Study or subgroup	Dexamphetamine N	Mean(SD)	Paroxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Weiss 2006	23	20.78 (9.65)	26	24.71 (9.47)		-0.40 [-0.97, 0.16]

Analysis 16.2. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 2 Proportion of participants achieving a CGI-Improvement score of 1 or 2.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 2 Proportion of participants achieving a CGI-Improvement score of 1 or 2

Study or subgroup	Dexamphetamine n/N	Paroxetine n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Weiss 2006	15/23	4/24		3.91 [1.52, 10.05]

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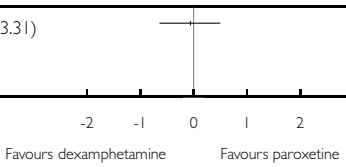
Analysis 16.3. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 3 Global functioning.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 3 Global functioning

Study or subgroup	Dexamphetamine N	Mean(SD)	Paroxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Weiss 2006	23	60 (15.89)	24	61.04 (13.31)		-0.07 [-0.64, 0.50]



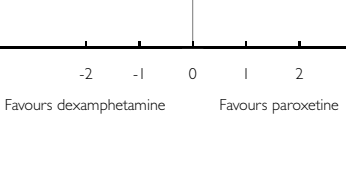
Analysis 16.4. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 4 Depressive symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 4 Depressive symptoms

Study or subgroup	Dexamphetamine N	Mean(SD)	Paroxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Weiss 2006	23	7.56 (7.25)	24	4.83 (4.26)		0.45 [-0.13, 1.03]



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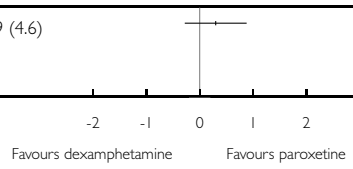
Analysis 16.5. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 5 Anxiety symptoms.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 5 Anxiety symptoms

Study or subgroup	Dexamphetamine N	Mean(SD)	Paroxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Weiss 2006	23	9.17 (7.8)	24	7.29 (4.6)		0.29 [-0.28, 0.87]



Analysis 16.6. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 6 Retention in treatment.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 6 Retention in treatment

Study or subgroup	Dexamphetamine n/N	Paroxetine n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Weiss 2006	14/23	15/24		0.97 [0.62, 1.53]

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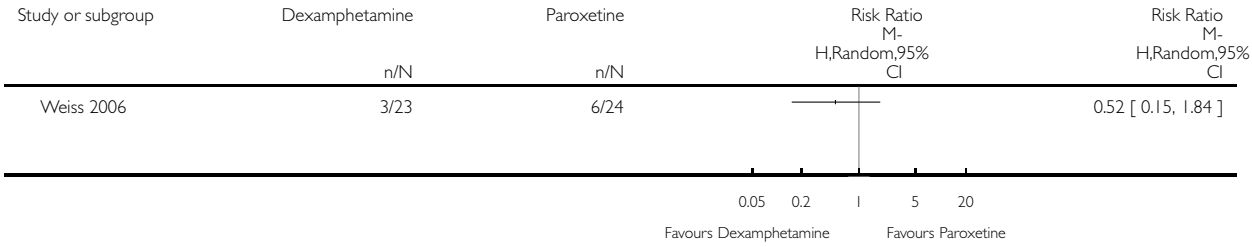
Analysis 16.7. Comparison 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults, Outcome 7 Proportion of participants withdrawn owing to any adverse event.

Review: Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 16 Amphetamines vs paroxetine for adult attention deficit hyperactivity disorder (ADHD) in adults

Outcome: 7 Proportion of participants withdrawn owing to any adverse event



ADDITIONAL TABLES

Table 1. Participants' baseline characteristics

Characteristic	Descriptive statistics	N studies (N patients)
Gender: male	N = 1435 (57.2%)	19 (2507)
Age	Mean = 35.3 (range = 20.2 to 41.2) years	19 (2507)
Race: Caucasian	N = 2006 (84.5%)	15 (2373)
Combined ADHD	N = 1341 (78.8%)	11 (1701)
Predominantly inattentive ADHD	N = 344 (20.2%)	
Predominantly hyperactive/impulsive ADHD	N = 28 (1.6%)	
Comorbid SUD as inclusion criterion	N = 158 (6.3%)	19 (2507)
Comorbid depressive disorders as inclusion criteria	N = 0	19 (2507)
Comorbid anxiety disorders as inclusion criteria	N = 0	19 (2507)
Treated previously with stimulants	N = 306 (41.1%)	8 (744)

ADHD: attention deficit hyperactivity disorder.

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N: number.
SUD: substance use disorder.

APPENDICES

Appendix 1. Search strategies from 2010 onwards

Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library

#1[mh ^"attention deficit and disruptive behavior disorders"]
#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]
#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
#7(impulsiv* or inattentiv* or inattention*)
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*)
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
#11(hyperactiv* or hyper next activ*)
#12{or #1-#11}
#13[mh Amphetamines]
#14(amphetamin* or amfetamin* or anfetamin*)
#15benzedrin*
#16(dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin*)
#17(dex next amphetamin* or dex next amfetamin* or dextro next amphetamin* or dextro next amfetamin*)
#18(lisdexamphetamin* or lisdexamfetamin*)
#19(lis next dexamphetamin* or lis next dexamfetamin*)
#20(Adderall or Dexedrine or Elvanse or Vyvanse)
#21{or #13-#20}
#22#12 and #21 in Trials

MEDLINE Ovid

1 "attention deficit and disruptive behavior disorders"/
2 attention deficit disorder with hyperactivity/
3 conduct disorder/
4 ADHD.tw,kw.
5 ADDH.tw,kw.
6 ADHS.tw,kw.
7 ("AD/HD" or HKD).tw,kw.
8 TDAH.tw,kw.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$).tw,kw.

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14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
15 (hyperactiv$ or hyper-activ$).tw,kw.
16 or/1-15
17 exp Amphetamines/
18 (amphetamin$ or amfetamin$ or anfetamin$).mp.
19 benzedrin$.mp.
20 (dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or dexedrin$).mp.
21 (dex-amphetamine or dex-amfetamine or dextro-amphetamine or dextro-amfetamine).mp.
22 (lisdexamphetamin$ or lisdexamfetamin$).mp.
23 (lis-dexamphetamin$ or lis-dexamfetamin$).mp.
24 (Adderall or Dexedrine or Elvanse or Vyvanse).mp.
25 or/17-24
26 16 and 25
27 randomized controlled trial.pt.
28 controlled clinical trial.pt.
29 randomi#ed.ab.
30 placebo$.ab.
31 drug therapy.fs.
32 randomly.ab.
33 trial.ab.
34 groups.ab.
35 or/27-34
36 exp animals/ not humans.sh.
37 35 not 36
38 26 and 37

MEDLINE In-Process and Other Non-indexed Citations Ovid

1 ("AD/HD" or HKD).mp.
2 TDAH.mp.
3 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).mp.
4 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).mp.
5 (impulsiv$ or inattentiv$ or inattention$).mp.
6 (hyperkin$ or hyper-kin$).mp.
7 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).mp.
8 (hyperactiv$ or hyper-activ$).mp.
9 or/1-8
10 (amphetamin$ or amfetamin$ or anfetamin$).mp.
11 benzedrin$.mp.
12 (dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or dexedrin$).mp.
13 (dex-amphetamine or dex-amfetamine or dextro-amphetamine or dextro-amfetamine).mp.
14 (Adderall or Dexedrine or Elvanse or Vyvanse).mp.
15 or/10-14
16 random$.mp.
17 control$.mp.
18 placebo$.mp.
19 trial.mp.
20 groups.mp.
21 or/16-20
22 9 and 15 and 21

MEDLINE Epub Ahead of Print Ovid

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1 ("AD/HD" or HKD).mp.
2 TDAH.mp.
3 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).mp.
4 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).mp.
5 (impulsiv$ or inattentiv$ or inattention$).mp.
6 (hyperkin$ or hyper-kin$).mp.
7 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).mp.
8 (hyperactiv$ or hyper-activ$).mp.
9 or/1-8
10 (amphetamin$ or amfetamin$ or anfetamin$).mp.
11 benzedrin$.mp.
12 (dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or dexedrin$).mp.
13 (dex-amphetamine or dex-amfetamine or dextro-amphetamine or dextro-amfetamine).mp.
14 (Adderall or Dexedrine or Elvanse or Vyvanse).mp.
15 or/10-14
16 random$.mp.
17 control$.mp.
18 placebo$.mp.
19 trial.mp.
20 groups.mp.
21 or/16-20
22 9 and 15 and 21

Embase Ovid

1 attention deficit disorder/
2 hyperactivity/
3 conduct disorder/
4 ADHD.tw,kw.
5 ADDH.tw,kw.
6 ADHS.tw,kw.
7 ("AD/HD" or HKD).tw,kw.
8 TDAH.tw,kw.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
12 hyperkinesis/ (3903)
13 (hyperkin$ or hyper-kin$ or hkd).tw,kw.
14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
15 (hyperactiv$ or hyper-activ$).tw,kw.
16 or/1-15
17 exp amphetamine derivative/
18 (amphetamin$ or amfetamin$ or anfetamin$).mp.
19 benzedrin$.mp.
20 (dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or dexedrin$).mp.
21 (dex-amphetamine or dex-amfetamine or dextro-amphetamine or dextro-amfetamine).mp.
22 (lisdexamphetamin$ or lisdexamfetamin$).mp.
23 (lis-dexamphetamin$ or lis-dexamfetamin$).mp.
24 (Adderall or Dexedrine or Elvanse or Vyvanse).mp.
25 or/17-24
26 16 and 25
27 Randomized controlled trial/
28 controlled clinical trial/

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29 Single blind procedure/
30 Double blind procedure/
31 triple blind procedure/
32 Crossover procedure/
33 (crossover or cross-over).tw.
34 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
35 Placebo/
36 placebo.tw.
37 prospective.tw.
38 factorial$.tw.
39 random$.tw.
40 assign$.ab.
41 allocat$.tw.
42 volunteer$.ab.
43 or/27-42
44 26 and 43

PsycINFO Ovid

1 exp attention deficit disorder/
2 exp Behavior Problems/
3 adhd.tw.
4 addh.tw.
5 adhs.tw.
6 "ad/hd".tw.
7 TDAH.tw.
8 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw.
9 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw.
10 Impulsiveness/
11 (impulsiv$ or inattentiv$ or inattention$).tw.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$ or hkd).tw.
14 (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
15 (hyperactiv$ or hyper-activ$).tw.
16 or/1-15
17 exp amphetamine/
18 (amphetamin$ or amfetamin$ or anfetamin$).mp.
19 benzedrin$.mp.
20 (dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or dexedrin$).mp.
21 (dex-amphetamine or dex-amfetamine or dextro-amphetamine or dextro-amfetamine).mp.
22 (lisdexamphetamin$ or lisdexamfetamin$).mp.
23 (lis-dexamphetamin$ or lis-dexamfetamin$).mp.
24 (Adderall or Dexedrine or Elvanse or Vyvanse).mp.
25 or/17-24
26 16 and 25
27 clinical trials/
28 random$.tw.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
30 (crossover$ or "cross over$").tw.
31 trial$.tw.
32 group$.ab.
33 control.ab.
34 exp program evaluation/

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35 treatment effectiveness evaluation/
36 treatment outcome clinical trial.md.
37 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
38 (allocat$ or assign$).tw.
39 placebo.ab.
40 or/27-39
41 26 and 40

CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

S1 (MH "Attention Deficit Hyperactivity Disorder")
S2 ADHD
S3 ADDH
S4 ADHS
S5 TDAH
S6 "AD/HD" or HKD
S7 ((attention* or behav*) N3 (defic* or dysfunc* or disorder*))
S8 ((disrupt* N3 disorder*) or (disrupt* N3 behav*) or (defian* N3 disorder*) or (defian* N3 behav*))
S9 (impulsiv* or inattentiv* or inattention*)
S10 (MH "Hyperkinesis")
S11 hyperkin* or hyper-kin*)
S12 (minimal N3 brain N3 (disorder* or dysfunct* or damage*))
S13 hyperactiv* or hyper-activ*
S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15 (MH "Amphetamines+")
S16 (amphetamin* or amfetamin* or anfetamin*)
S17 benzedrin*
S18 (dexamphetamin* or dexamfetamin$ or dextroamphetamin* or dextroamfetamin*)
S19 (dex-amphetamine or dex-amfetamin* or dextro-amphetamin* or dextro-amfetamin*)
S20 lisdexamphetamin* or lisdexamfetamin*
S21 lis-dexamphetamin* or lis-dexamfetamin*
S22 (Adderall or Dexedrine or Elvanse or Vyvanse)
S23 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S24 S14 AND S23
S25 (MH "Clinical Trials+")
S26 MH random assignment
S27 (MH "Meta Analysis")
S28 (MH "Crossover Design")
S29 (MH "Quantitative Studies")
S30 PT randomized controlled trial
S31 PT Clinical trial
S32 (clinical trial*) or (control* N2 trial*)
S33 ("follow-up study" or "follow-up research")
S34 (prospectiv* study or prospectiv* research)
S35 (evaluat* N2 study or evaluat* N2 research)
S36 (MH "Program Evaluation")
S37 (MH "Treatment Outcomes")
S38 TI(single N2 mask* or single N2 blind*) OR AB(single N2 mask* or single N2 blind*)
S39 TI((doubl* N2 mask*) or (doubl* N2 blind*)) OR AB((doubl* N2 mask*) or (doubl* N2 blind*))
S40 TI ((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*)) OR AB((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*)
S41 random* N2 assign* OR random* N2 allocat*

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S42 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S43 S24 AND S42

Science Citation Index (SCI) and Social Science Citation Index (SSCI), both Web of Science

#19 #18 AND #17
#18 TS=(RANDOM* OR TRIAL* OR GROUP* OR CONTROL* OR PLACEBO OR BLIND*)
#17 #16 AND #8
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
#15 TS=(Adderall or Dexedrine or Elvanse or Vyvanse)
#14 TS=(lis-dexamphetamin* or lis-dexamfetamin*)
#13 TS=(lisdexamphetamin* or lisdexamfetamin*)
#12 TS=(dex-amphetamin* or dex-amfetamin* or dextro-amphetamin* or dextro-amfetamin*)
#11 TS=(dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin*)
#10 TS=benzedrin*
#9 TS=(amphetamin* or amfetamin* or anfetamin*)
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 TS=(hyperactiv* or hyper-activ*)
#6 TS=(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
#5 TS=(hyperkin* or hyper-kin*)
#4 TS=(impulsiv* or inattentiv* or inattention*)
#3 TS=((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
#2 TS=(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
#1 TS=((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))

Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H), both Web of Science

#19 #18 AND #17
#18 TS=(RANDOM* OR TRIAL* OR GROUP* OR CONTROL* OR PLACEBO OR BLIND*)
#17 #16 AND #8
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
#15 TS=(Adderall or Dexedrine or Elvanse or Vyvanse)
#14 TS=(lis-dexamphetamin* or lis-dexamfetamin*)
#13 TS=(lisdexamphetamin* or lisdexamfetamin*)
#12 TS=(dex-amphetamin* or dex-amfetamin* or dextro-amphetamin* or dextro-amfetamin*)
#11 TS=(dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin*)
#10 TS=benzedrin*
#9 TS=(amphetamin* or amfetamin* or anfetamin*)
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 TS=(hyperactiv* or hyper-activ*)
#6 TS=(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
#5 TS=(hyperkin* or hyper-kin*)
#4 TS=(impulsiv* or inattentiv* or inattention*)
#3 TS=((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
#2 TS=(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
#1 TS=((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))

Cochrane Database of Systematic Reviews (CDSR), part of the Cochrane Library

#1[mh ^"attention deficit and disruptive behavior disorders"]
#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]

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#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH):ti,ab,kw
#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#7(impulsiv* or inattentiv* or inattention*):ti,ab,kw
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*):ti,ab,kw
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#11(hyperactiv* or hyper next activ*):ti,ab,kw
#12{or #1-#11}
#13[mh Amphetamines]
#14(amphetamin* or amfetamin* or anfetamin*):ti,ab,kw
#15benzedrin*:ti,ab,kw
#16(dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin*):ti,ab,kw
#17(dex next amphetamin* or dex next amfetamin* or dextro next amphetamin* or dextro next amfetamin*):ti,ab,kw
#18(lisdexamphetamin* or lisdexamfetamin*):ti,ab,kw
#19(lis next dexamphetamin* or lis next dexamfetamin*):ti,ab,kw
#20(Adderall or Dexedrine or Elvanse or Vyvanse):ti,ab,kw
#21{or #13-#20} in Cochrane Reviews (Reviews and Protocols)

Database of Abstracts of Reviews of Effects (DARE), part of the Cochrane Library

#1[mh ^"attention deficit and disruptive behavior disorders"]
#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]
#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH):ti,ab,kw
#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#7(impulsiv* or inattentiv* or inattention*):ti,ab,kw
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*):ti,ab,kw
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#11(hyperactiv* or hyper next activ*):ti,ab,kw
#12{or #1-#11}
#13[mh Amphetamines]
#14(amphetamin* or amfetamin* or anfetamin*):ti,ab,kw
#15benzedrin*:ti,ab,kw
#16(dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin*):ti,ab,kw
#17(dex next amphetamin* or dex next amfetamin* or dextro next amphetamin* or dextro next amfetamin*):ti,ab,kw
#18(lisdexamphetamin* or lisdexamfetamin*):ti,ab,kw
#19(lis next dexamphetamin* or lis next dexamfetamin*):ti,ab,kw
#20(Adderall or Dexedrine or Elvanse or Vyvanse):ti,ab,kw
#21{or #13-#20}
#22#12 and #21 in Other Reviews

WorldCat (www.worldcat.org)

'kw:(adhd OR "attention deficit" OR hyper*) AND (amfetamin* OR amphetamin*) AND KW:(random* OR trial* OR placebo* OR control* OR blind*)' >'Thesis/dissertation'

Clinicaltrials.gov (clinicaltrials.gov)

Advanced search ADHD OR hyperactive OR attention deficit | AMFETAMINES OR amphetamines OR dexamphetamine or dexamfetamine or dextroamphetamine or dextroamfetamine OR lisdexamphetamin OR lisdexamfetamin* OR Adderall OR Dexedrine OR Elvanse OR Vyvanse | Adult, Senior

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World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en)

Advanced search Condition: ADHD OR hyperactive OR attention deficit AND Intervention:amfetamin* OR amphetamin* OR dexamphetamine or dexamfetamine or dextroamphetamine or dextroamfetamine OR lisdexamphetamin OR lisdexamfetamin* OR Adderall OR Dexedrine OR Elvanse OR Vyvanse.

AUTOMATIC SYNONYMS included in search: ADDH, ATTENTION DEFICIT DIS WITH HYPERACTIVITY, ATTENTION DEFICIT DISORDER, ATTENTION DEFICIT DISORDER OF CHILDHOOD WITH HYPERACTIVITY, ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY, ATTENTION DEFICIT DISORDERS WITH HYPERACTIVITY, ATTENTION DEFICIT HYPERACTIVITY DIS, ATTENTION DEFICIT HYPERACTIVITY DISORDER, ATTENTION DEFICIT HYPERACTIVITY DISORDERS, ATTENTION DEFICIT-HYPERACTIVITY DISORDER, ATTENTION-DEFICIT DISORDER, COMBINED TYPE, ATTENTION-DEFICIT DISORDER, PREDOMINANTLY HYPERACTIVE-IMPULSIVE TYPE, ATTN
DEFICIT W HYPERACT, CHILDHOOD HYPERKINETIC SYNDROME, HYPERACTIVE CHILD SYNDROME, HYPERACTIVITY DISORDER NOS, HYPERACTIVITY DISORDER, PREDOMINANTLY HYPERACTIVE-IMPULSIVE TYPE, HYPERACTIVITY
OF CHILDHOOD, HYPERKINETIC SYND NOS, HYPERKINETIC SYNDROME, HYPERKINETIC SYNDROME NOS, HYPERKINETIC SYNDROME OF CHILDHOOD, SYNDROME HYPERKINETIC, SYNDROMES, HYPERKINETIC, UNSPECIFIED
HYPERKINETIC SYNDROME OF CHILDHOOD, adhd: - amphetamine a d - d amphetamine - d-amphetamine - d-amphetamine sulfate - dexamfetamine - dexamphetamine - dexedrine - dextro amphetamine -
dextro-amphetamine - dextroamphetamine - lisdexamphetamin - dextroamfetamine - lisdexamfetamin - amphetamine a d - d amphetamine - d-amphetamine - dexamfetamine - dextro amphetamine -
dextro-amphetamine - dextroamphetamine - dexamphetamine - amphetamine a d - d amphetamine - d-amphetamine - dexamphetamine - dextro amphetamine - dextro-amphetamine - dextroamphetamine -
dexamfetamine - amphetamin - celltech brand of dextroamphetamine sulfate - dextroamphetamine - dextroamphetamine sulfate - glaxosmithkline brand of dextroamphetamine sulfate - mallinckrodt
brand of dextroamphetamine sulfate - dexedrine - amfetamin - dextroamphetamine-amphetamine - adderall - vyvanse - elvanse

Appendix 2. Search strategies up to 2010

Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library

#1 MeSH descriptor Amphetamines explode all trees
#2 adderall
#3 lisdexamphetamine or lisdexamfetamine or vyvanse
#4 amphetamine* or amfetamine* or amphetamine or amfetamine or benzedrine
#5 dexamphetamine or dexamfetamine or dextroamphetamine or dextroamfetamine or dexedrine
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Attention Deficit Disorder with Hyperactivity explode all trees
#8 adhd
#9 addh
#10 adhs
#11 hyperactiv*
#12 hyperkin*
#13 attention* AND deficit*
#14 attention* AND disorder*
#15 brain dysfunction*
#16 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#6 AND #16)

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PubMed

("amphetamine"[MeSH Terms] OR Adderall OR lisdexamphetamine OR lisdexamfetamine OR vyvanse OR amphetamine* OR amfetamine* OR amphetamine OR amfetamine OR benzedrine OR dexamphetamine OR dexamfetamine OR "dextroamphetamine"[MeSH Terms] OR dextroamfetamine OR dexedrine) AND ("attention deficit disorder with hyperactivity"[MeSH Terms] OR ADHD OR ADDH OR ADHS OR "attention deficit" OR "brain dysfunction") AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Embase Ovid

1 Attention Deficit Disorder with Hyperactivity/
2 adhd.tw.
3 addh.tw.
4 adhs.tw.
5 hyperactiv$.tw.
6 hyperkin$.tw.
7 attention deficit$.tw.
8 brain dysfunction.tw.
9 or/1-8
10 exp Amphetamine/
11 adderall.tw.
12 lisdexamphetamine.tw.
13 lisdexamfetamine.tw.
14 vyvanse.tw.
15 amphetamine$.tw.
16 amfetamine*.tw.
17 benzedrine.tw.
18 dexamphetamine.tw.
19 dexamfetamine.tw.
20 exp Dextroamphetamine/
21 dextroamfetamine.tw.
22 dexedrine.tw.
23 or/10-22
24 9 and 23
25 random$.tw.
26 factorial$.tw.
27 crossover$.tw.
28 cross over$.tw.
29 cross-over$.tw.
30 placebo$.tw.
31 (doubl$ adj blind$).tw.
32 (singl$ adj blind$).tw.
33 assign$.tw.
34 allocat$.tw.
35 volunteer$.tw.
36 Crossover Procedure/
37 double-blind procedure.tw.
38 Randomized Controlled Trial/
39 Single Blind Procedure/
40 or/25-39
41 24 and 40

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CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

S40 S23 and S39
S39 S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38
S38 allocat* random*
S37 (MH "Quantitative Studies")
S36 (MH "Placebos")
S35 placebo*
S34 random* allocat*
S33 (MH "Random Assignment")
S32 (Randomi?ed control* trial*)
S31 (singl* mask*)
S30 (doubl* mask*)
S29 (tripl* mask*)
S28 (trebl* mask*)
S27 (trebl* blind*)
S26 (tripl* blind*)
S25 (doubl* blind*)
S24 (singl* blind*)
S23 S9 and S22
S22 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S21 dexedrine
S20 dextroamphetamine
S19 dexamfetamine
S18 dexamphetamine
S17 benzedrine
S16 amfetamine*
S15 amphetamine*
S14 vyvanse
S13 lisdexamfetamine
S12 lisdexamphetamine
S11 adderall
S10 (MH "Amphetamine+")
S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8
S8 brain dysfunction
S7 attention deficit*
S6 hyperkin*
S5 hyperactiv*
S4 adhs
S3 addh
S2 adhd
S1 (MH "Attention Deficit Hyperactivity Disorder")

PsycINFO Ovid

1 Attention Deficit Disorder with Hyperactivity/
2 adhd.tw.
3 addh.tw.
4 adhs.tw.
5 hyperactiv$.tw.
6 hyperkin$.tw.
7 attention deficit$.tw.
8 brain dysfunction.tw.
9 or/1-8

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10 exp Amphetamine/
11 adderall.tw.
12 lisdexamphetamine.tw.
13 lisdexamfetamine.tw.
14 vyvanse.tw.
15 amphetamine$.tw.
16 amfetamine*.tw.
17 benzedrine.tw.
18 dexamphetamine.tw.
19 dexamfetamine.tw.
20 exp Dextroamphetamine/
21 dextroamfetamine.tw.
22 dexedrine.tw.
23 or/10-22
24 9 and 23
25 Treatment Effectiveness Evaluation/
26 exp Treatment Outcomes/
27 Psychotherapeutic Outcomes/
28 PLACEBO/
29 exp Followup Studies/
30 placebo$.tw.
31 random$.tw.
32 comparative stud$.tw.
33 randomi#ed controlled trial$.tw.
34 (clinical adj3 trial$).tw.
35 (research adj3 design).tw.
36 (evaluat$ adj3 stud$).tw.
37 (prospectiv$ adj3 stud$).tw.
38 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
39 control$.tw.
40 39 or 31 or 29 or 37 or 36 or 32 or 25 or 30 or 26 or 38 or 34 or 28 or 27 or 35 or 33
41 24 and 40

Clinicaltrials.gov (clinicaltrials.gov)

("amphetamine" OR Adderall OR lisdexamphetamine OR lisdexamfetamine OR vyvanse OR amphetamine* OR amfetamine* OR amphetamine OR amfetamine OR benzedrine OR dexamphetamine OR dexamfetamine OR "dextroamphetamine" OR dextroamfetamine OR dexedrine) AND ("attention deficit disorder with hyperactivity" OR ADHD OR ADDH OR ADHS OR "attention deficit" OR "brain dysfunction")

Appendix 3. Data to be extracted from included studies

Study description and funding

Author
Year of publication
Country
Author affiliation (pharmaceutical industry (Yes/No))
Study funding (pharmaceutical industry (Yes/No))

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Methods

Sequence generation
Allocation concealment
Blinding of patients/clinicians/therapists/assessors
Design (cross-over/parallel groups)
Design (single site/multiple sites)
Study length (from randomisation to treatment completion)
Number of participants
Handling of dropouts (intention-to-treat (ITT) vs non-ITT)
Outcomes (including description of instruments used)

Participants

Inclusion/exclusion criteria
Gender (% male)
Age (mean, standard deviation (SD))
Race (% Caucasian, % African-American, % other)
Employment status (% unemployed)
Prior ADHD treatment (Yes/No), with psychostimulants (Yes/No)
Type of ADHD (% with inattentive subtype, % hyperactive subtype, % combined subtype)
Comorbid disorders (% with comorbid psychiatric disorders)

Intervention

Type of amphetamine
Dose
Pharmaceutical presentation
Assessment of compliance
Adjunctive psychological interventions

Outcomes

1. Achievement of significant clinical improvement. Although several definitions of significant improvement of ADHD symptom are used, we will prefer a "30% reduction of the ADHD severity". When any study uses a different definition, we will collect and use it also (% patients achieving a significant clinical improvement)
2. ADHD severity score (note: these data will be collected for each instrument used to assess ADHD symptom severity)
3. Clinical impression of severity (% patients achieving a Clinical Global Impression (CGI) - Severity score of one or two at study end, mean (SD) CGI-Severity at the end of the study)
4. Clinical impression of improvement (% patients achieving a CGI-Improvement score of one or two at study end, mean (SD) CGI-Improvement at the end of the study)
5. Global functioning (mean (SD) score at study end)
6. Anxiety symptom severity (mean (SD) anxiety score at study end)
7. Depressive symptom severity (mean (SD) depression score at study end)
8. Number of participants withdrawn owing to adverse events (% participants withdrawn owing to any adverse event and % participants withdrawn owing to a cardiovascular adverse event)
9. Abuse of study medication (% participants who abused study medication)
10. Retention in treatment (% participants who completed the study)

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Appendix 4. Criteria for assigning 'Risk of bias' judgements

Sequence generation

Description: the method used to generate the allocation sequence is described in sufficient detail to assess whether it should have produced comparable groups.
Review authors' judgement: was the allocation concealment sequence adequately generated?

Allocation concealment

Description: the method used to conceal the allocation sequence is described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment.
Review authors' judgement: was allocation adequately concealed?

Blinding of participants and personnel

Description: measures used to keep the intervention blinded to participants and personnel are described in sufficient detail to assess the suitability of methods used to prevent knowledge of the allocated intervention.
Review authors' judgement: was knowledge of the allocated intervention adequately prevented during the study?

Blinding of outcome assessment

Description: measures used to keep the intervention blinded to outcome assessors are described in sufficient detail to assess the suitability of methods used to prevent knowledge of the allocated intervention.
Review authors' judgement: was knowledge of the allocated intervention adequately prevented during the study?

Incomplete outcome data

Description: if studies did not report intention-to-treat analyses, we attempted to obtain the missing data by contacting the study authors. We extracted and reported data on attrition and exclusions as well as numbers involved (compared with total). We also provided reasons for attrition/exclusion when reported or obtained from investigators, and incorporated any re-inclusions in analyses performed.
Review authors' judgement: were incomplete data dealt with adequately by the reviewers? (see also Dealing with missing data)

Selective outcome reporting

Description: we attempted to assess the possibility of selective outcome reporting by investigators.
Review authors' judgement: are reports of the study free of the suggestion of selective outcome reporting?
We attempted to deal with the possibility of selective outcome reporting by searching for the original protocols of each included study in trial registries and comparing these (when available) with the list of outcomes in the methods section of the final report. We constructed a table to present an outcomes matrix to compare relevant outcomes between studies. In cases where we suspected selective outcome reporting, we contacted the study author.

Other bias

Description: we assessed imbalanced baseline characteristics, blocked randomisations, and deviations from protocol, as well as the possibility of carry-over effect in cross-over trials.
Review authors' judgement: was there any evidence of other potential sources of bias?
We considered a study to be (1) at low risk of bias overall if all key domains were judged at low risk of bias; (2) at unclear risk of bias overall if one or more domains were judged at unclear risk of bias and all other domains were judged at low risk of bias; and (3) at high risk of bias overall if one or more domains were judged at high risk of bias (Higgins 2017a).

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WHAT'S NEW

Last assessed as up-to-date: 21 August 2017.

Date	Event	Description
27 September 2017	New citation required but conclusions have not changed	12 new studies included in the review; no changes made to the conclusions
21 August 2017	New search has been performed	Review updated following a new search in July 2016 and a top-up search in August 2017

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 6, 2011

Date	Event	Description
8 December 2010	Amended	Study author contact details updated

CONTRIBUTIONS OF AUTHORS

Xavier Castells (XC) and Ruth Cunill (RC) designed the review.

XC and RC wrote the background.

XC and RC wrote the methods, results, discussion, and conclusions with input from Lídia Blanco-Silvente (LB).

XC and RC selected studies.

XC, RC, and LB extracted data.

XC and RC conducted the statistical analyses.

XC is the guarantor for the review.

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DECLARATIONS OF INTEREST

Xavier Castells received a research grant for 'Improving the scientific productivity' (MPCUdG2016/ref50) from the Universitat de Girona, Spain.

Ruth Cunill - none known.

Lídia Blanco-Silvente has a pre-doctoral research contract (IFUdG2015/17) with the Universitat de Girona, Spain.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- Universitat de Girona, Spain.

Grants (MPCUdG2016/ref50) to Xavier Casatells and (IFUdG2015/17) Lídia Blanco-Silvente

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See our protocol (Castells 2009a).

1. Review authors

i) Josep Antoni Ramos-Quiroga, Rosa Bosch, Mariana Nogueira, and Miguel Casas left the review author team and were replaced by Lídia Blanco-Silvente and Ruth Cunill.

2. Types of outcome measures

i) The primary study outcome was initially "Change in the severity of ADHD symptoms assessed by a standardised instrument". However, we found that efficacy was studied by means of continuous outcome variables (change score, for example, change in the ADHD symptom severity score from baseline to study completion; and endpoint score, for example, ADHD symptom severity score at study completion), as well as binary ones (for example, proportion of patients achieving a reduction of at least 30% in the severity of ADHD symptoms), and few studies used the same efficacy outcome, making the meta-analysis of different studies poor. To allow the combination of the highest number of studies, we redefined the primary efficacy outcome to "ADHD symptom severity". This outcome combined studies reporting change scores or endpoint scores.

ii) The first version of this review - Castells 2011a - included only a small number of studies, so we conducted a post hoc analysis by aggregating all available data from studies irrespective of the reported efficacy outcome. We named this outcome "Efficacy for ADHD symptoms" and combined continuous and binary data on efficacy outcomes. We did not perform this analysis in this update because we included a considerably greater number of studies and were able to combine the results on primary study outcomes from several clinical trials.

iii) We changed the outcome "attrition" to "retention".

3. Electronic searches

i) To comply with MECIR conduct standards (Higgins 2016), which were introduced after the first version of this review was published (Castells 2011a), we searched a number of additional databases: MEDLINE In-Process and Other Non-Indexed Citations; MEDLINE Epub Ahead of Print (both these segments are updated daily); Science Citation Index; and Social Science Citation Index, We also searched for grey literature (via Conference Proceedings Citation Index - Science; Conference Proceedings Citation Index - Social Science & Humanities; and WorldCat) and sources of other reviews (*Cochrane Database of Systematic Review*s and Database of Abstracts of Reviews of Effects).

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4. Data collection and analysis

i) When appropriate, we updated our references to the most recent chapters of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

5. Assessment of risk of bias in included studies

i) In this update of the review, we also assessed the overall risk of bias within studies (Higgins 2017a), to facilitate our evaluation of the quality of evidence. We added the following paragraph to Appendix 4: "We considered a study to be: 1) at low risk of bias overall if all the key domains were judged at low risk of bias; 2) at unclear risk of bias overall if one or more domains were judged at unclear risk of bias and all other domains were judged at low risk of bias and; 3) at high risk of bias overall if one or more domains were judged at high risk of bias (Higgins 2017a)."

6. Assessment of heterogeneity

i) The protocol established that heterogeneity would be defined on the basis of the P value of the heterogeneity test (Castells 2009a). According to this method, heterogeneity is present or absent. It is more suitable to calculate the amount of heterogeneity using the I^2 statistic, which indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity (Higgins 2017b).

7. Subgroup analysis and investigation of heterogeneity

i) This section was insufficiently described in the protocol (Castells 2009a). In the previous version of this review published in 2011 (Castells 2011a), we broadened this section and explained the reasons for not doing some of our prespecified subgroup analyses. In the previous version of the review (Castells 2011a), we were unable to perform a subgroup analysis for comorbidity because data were insufficient, but as the number of included studies in this update is substantially larger, we were able to perform the analysis. However, we were not able to compare industry-sponsored trials to independent trials.

8. Sensitivity analysis

i) We planned to run a sensitivity analysis excluding any study rated at high or unclear risk of bias on any domain of the Cochrane 'Risk of bias' tool (Higgins 2017a). However, we were unable to perform this analysis as no study met this criterion because it is unclear whether blinding can be achieved when amphetamines are compared to placebo. Instead, we used our assessments for incomplete outcome data and other potential sources of bias, whose scores showed between-study variability, and conducted a sensitivity analysis that included only studies scoring low risk of bias on these specific domains.

ii) We conducted three post hoc sensitivity analyses: (1) we calculated the effect size of cross-over studies by borrowing the correlation coefficient from Taylor 2000 (see Unit of analysis issues); (2) we calculated the pooled risk difference for the outcomes "proportion of patients withdrawn due to AE" and "proportion of patients withdrawn due to cardiovascular AE" because this analysis allows for inclusion of studies that had no events for these outcomes; and (3) we excluded from the analysis one cross-over study (Spencer 2001), which had a carry-over effect, to determine wether the carry-over effect may have biased the results of this review. We did not perform this sensitivity analysis for the outcome "retention in treatment" because results from the first study period were available and, therefore, there was no risk of a carry-over effect-related bias for this outcome.

9. Data synthesis

i) The methods used to aggregate data have been explained in greater detail than in the published protocol (Castells 2009a), which described only the type of statistical model used.

10. Effects of interventions

i) In contrast to the previous version of this review (Castells 2011a), we did not conduct a post hoc analysis that pooled together all available studies irrespective of the type of efficacy outcome. Nor did we conduct a second post hoc sensitivity analysis combining "AE-induced dropouts" with those events described as dropouts due to "loss to follow-up", "withdrawal of consent", and "unknown reason". In the previous review (Castells 2011a), these analyses had allowed the inclusion of a larger number of studies in the efficacy analysis. However, as the number of included studies is substantially larger in the present update, we think that these analyses are no longer justified.

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INDEX TERMS

Medical Subject Headings (MeSH)

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MeSH check words

Adult; Humans

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